DISORDERS OF TISSUE MASS AND CELL DIFFERENTIATION 1

Many disorders (including congenital defects in organ development, diseases of malnutrition and neoplasia) involve abnormalities of cell growth. Disorderly cell growth may result in an **excess** or **deficit of tissue** or an **abnormal pattern of tissue growth.**

Growth disturbances involve changes in the **number of cells** within a tissue or organ, the **size of the cells** and/or the **relationship between different cell populations**.

Many of the terms used to describe lesions of disordered cell growth are derived from the Greek words *trophe* (= food, nutrition) and *plastos* (= moulded, formed).

CONGENITAL DISORDERS OF TISSUE MASS

- **congenital = present at birth**

- simply an observational term
- implies nothing about the **cause** of the abnormality
- causes of congenital malformations include genetic abnormalities (either inherited or arising from spontaneous mutation) and exposure to teratogenic agents *in utero* (e.g. viruses, drugs, toxins, a deficiency of a vital nutrient, an excess of a nutrient etc.)

Clinical signs referable to the following developmental anomalies may appear early in life. The severity of the clinical disease and the life expectancy of the animal will depend on the organ/tissue involved and the degree to which organ/tissue function and functional reserve are decreased.

Agenesis

- **agenesis = complete failure of a tissue or organ to develop**

- e.g. renal agenesis – incompatible with post-natal life if bilateral
- e.g. testicular agenesis

Aplasia

- **aplasia = failure of a tissue or organ to grow**

- the tissue or organ is present but is small and rudimentary

- when aplasia affects a localised area of a tubular structure, it is termed **segmental aplasia**
- e.g. segmental aplasia of the small or large intestine
- e.g. segmental aplasia of a uterine horn

Hypoplasia

- **hypoplasia = failure of an organ or tissue to reach its normal size, i.e. incomplete growth**

- a developmental defect in the spectrum between agenesis and normal development

- the term hypoplasia is often used interchangeably with aplasia
- e.g. renal hypoplasia
- e.g. cerebellar hypoplasia
- e.g. testicular hypoplasia

Dysplasia

- **dysplasia = abnormal development resulting in disorganisation of cells and hence architectural distortion of a tissue or organ**

- this is the strictest definition of dysplasia and as such the term is used to describe developmental anomalies of the eye, skin, brain, kidneys and skeleton
- e.g. renal dysplasia
- e.g. chrondrodysplasia
- e.g. retinal dysplasia

- in Lecture 29, you will see that the term "dysplasia" is also used to describe acquired disorders in which there is disorderly or atypical proliferation of cells

Atresia

- **atresia = absence or closure of a normal opening**

- e.g. intestinal atresia
- e.g. atresia ani (imperforate anus)

ACQUIRED DISORDERS OF TISSUE MASS

Cells normally exist and function within a narrow range of physicochemical conditions (e.g. intracellular pH and electrolyte concentrations) closely controlled by the cells themselves. Under normal conditions, cells must constantly adapt to changes in their environment, e.g. changes in the composition of extracellular fluid or the arrival of endogenous chemical mediators. Maintenance of intracellular conditions compatible with **cell survival** and **normal function** despite physiological changes in the cell's environment is termed **normal homeostasis.**

If a cell is subjected to excessive physiological stress or to other adverse stimuli, it may undergo adaptation to escape injury (Figure 1). Such adaptation involves changes in the metabolic or other functional activity of the cell to create a new steady state that is compatible with cell survival despite persistence of the external stress(es). Adaptive functional changes are often associated with structural changes in the affected cells.

The main adaptive changes of cells are **atrophy, hypertrophy, hyperplasia** and **metaplasia**:

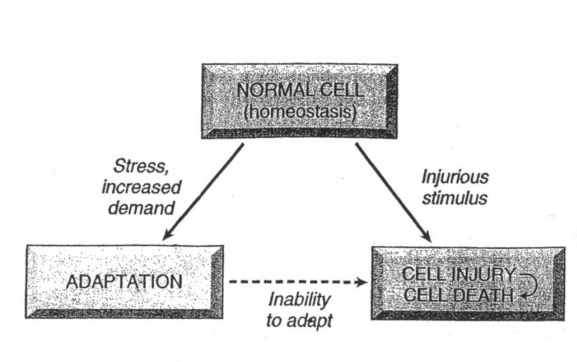
- **Atrophy** = a decrease in cell size or tissue mass after normal growth has been achieved

- **Hypertrophy** = an increase in cell size or 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

- **Metaplasia** = transformation of a mature differentiated cell type into another cell type

Figure 1



Reference: "Pathologic Basis of Veterinary Disease" – M. D. McGavin and J.F. Zachary (editors). 4th edition, Mosby Elsevier, St Louis, Missouri, 2007

ATROPHY

Atrophy is an **acquired adaptive decrease in size or mass**. Atrophy may occur at the level of cellular organelles, cells, tissues or entire organs and involves structures that are already fully developed (**do not confuse atrophy with hypoplasia**).

If sufficient numbers of cells atrophy, entire tissues or organs may shrink. The adverse stimuli that trigger cell atrophy may also cause death of some cells (via **apoptosis** or **oncotic necrosis**) which may contribute to the decrease in tissue mass. In other words, **an atrophic organ or tissue may contain both smaller cells and fewer cells**.

Atrophy can be **physiological** or **pathological**. The fundamental cell change is the same in both processes. Cell survival is achieved by a **decrease in cell size** and **functional activity**.

Causes of Atrophy

- triggers for cell/tissue atrophy are:

- decreased workload
- loss of innervation
- decreased blood supply
- loss of endocrine stimulation
- obstruction of secretory/drainage ducts
- inadequate nutrition
- ageing

Intracellular Events in Atrophy

- the biochemical pathways responsible for cell atrophy are incompletely understood
- what is known is that atrophy involves **decreased protein synthesis** and/or **increased protein catabolism**, and **increased autophagy** (**autophagocytosis**)

- misfolded or damaged cell proteins are degraded by the **ubiquitin-proteasome pathway**
- targeted proteins bind to **ubiquitin** (a heat shock protein) and are thence directed into a **proteasome** in which enzymatic degradation takes place

- damaged or effete cell organelles and adjacent cytoplasmic matrix are enveloped by an invagination of the cell membrane to form an **autophagosome** (**autophagic vacuole**) which then fuses with a lysosome to allow enzymatic digestion
- some of the autophagic vacuoles may be expelled from the cell via exocytosis
- others persist as **residual bodies** in which **lipofuscin** ("wear-and-tear pigment" or "age pigment") accumulates
- lipofuscin consists of polymers of lipids and phospholipids complexed with proteins
- represents an indigestible residue following peroxidation and polymerisation of unsaturated fatty acids of the phospholipid component of organelle membranes

Ultrastructural Appearance of Atrophy

- reduction in size and number of cellular organelles
- loss of ribosomes, endoplasmic reticulum and secretory granules
- increased numbers of **autophagic vacuoles** +/- **residual bodies** (which may contain electron-dense and lamellar lipofuscin)

Microscopic Appearance of Atrophy

- reduction in cell size may be difficult to appreciate if organs are diffusely affected
- crowding of small cells → false impression of tissue hypercellularity
- increased prominence of blood vessels due to condensation
- increased prominence of connective tissue; this may be due to both condensation of the original connective tissue and a genuine increase due to fibroplasia/fibrosis stimulated by the process responsible for the atrophy
- **fatty infiltration** (replacement of original tissue by adipose tissue) – especially in atrophic skeletal muscle, thymus, exocrine pancreas and mammary gland
- **lipofuscinosis** – intracellular accumulation of golden-brown lipofuscin granules, especially in atrophic myocardial fibres and neurons

Gross Appearance of Atrophy

- reduced size and weight of tissue or organ
- may be firmer than normal due to condensation of connective tissue +/- fibrosis
- may be paler than normal due to fibrosis or fibrofatty connective tissue replacement of the original parenchyma
- may be grossly discoloured brown-yellow due to lipofuscinosis (**"brown atrophy"**)
- if entire organs are affected, the organ capsule may appear wrinkled

Fate of Atrophic Cells

- atrophy is **potentially reversible**
- if the cause is removed, atrophic cells may revert to their normal structural and functional state by undergoing **physiological hypertrophy**
- if the cause is removed, atrophic organs may revert to their normal size by a combination of **cell hypertrophy and hyperplasia**
- if atrophy has been prolonged, complete return to normal may be impossible due to loss of cells and/or fibrosis

Examples of Physiological Atrophy

Involution of Lymphoid Organs

- e.g. thymic involution from puberty onwards
- e.g. senile atrophy of lymph nodes

Cyclic Changes in the Reproductive Tract

- especially in species with seasonal breeding cycles
- e.g. involution of the corpus luteum of the ovary during the oestrous cycle

Involution of Reproductive Organs

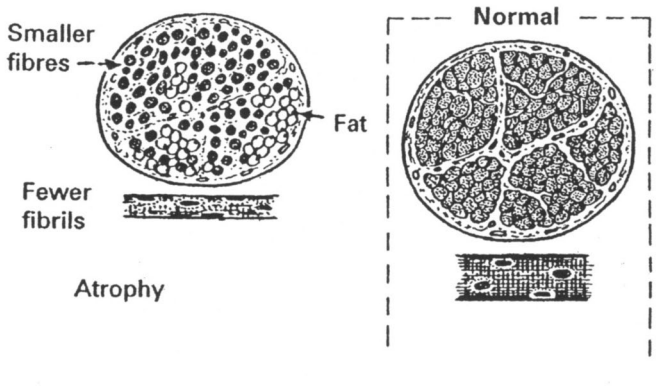
- e.g. involution of the uterus following parturition
- e.g. involution of the secretory parenchyma of the mammary gland following weaning of offspring

Examples of Pathological Atrophy

Decreased Workload

- e.g. disuse atrophy of skeletal muscles +/- bone (disuse osteoporosis) of limbs that are paralysed or immobilised long term (e.g. in plaster casts) (Figure 2)
- e.g. muscle and bone atrophy in astronauts

Figure 2



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

Loss of Innervation

- **denervation** (or **neurogenic**) **atrophy of skeletal muscle** is common in domestic animals
- e.g. atrophy of the left dorsal cricoarytenoid muscle in laryngeal hemiplegia ("roaring") in horses due to damage to the left recurrent laryngeal nerve
- e.g. radial or brachial nerve paralysis in small animals following car accidents

Decreased Blood Supply

- e.g. atrophy of hepatocytes if portal venous blood is diverted into the systemic circulation bypassing the liver (acquired portosystemic shunting)

- decreased blood supply often contributes to **pressure atrophy** of tissues compressed by tumours, cysts, abscesses or other space-occupying lesions
- e.g. pressure atrophy of the liver compressed by a chronically distended colon or rumen
- e.g. pressure atrophy of the brain due to expansile growth of a meningeal tumour
- e.g. pressure atrophy of epithelial cells of the inner renal medulla in hydronephrosis due to obstruction of urine outflow

Loss of Endocrine Stimulation

- a decrease in concentrations of trophic hormones → atrophy of the target organs
- e.g. atrophy of accessory sex glands such as the prostate following castration of male animals

Obstruction of Drainage

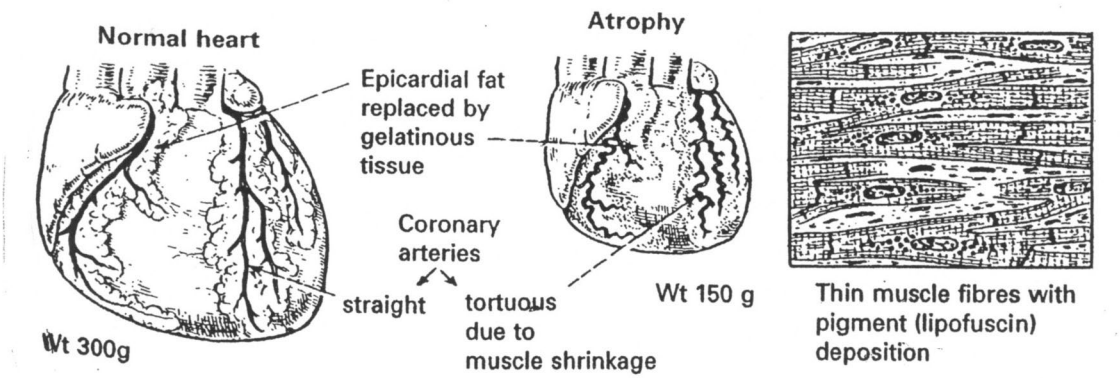
- e.g. atrophy of hepatic parenchyma due to obstruction of bile ducts
- e.g. atrophy of exocrine pancreatic parenchyma following obstruction of pancreatic ducts

- atrophy associated with duct obstruction is often compounded by atrophy of pressure and reduced blood supply associated with scarring (fibrosis)

Inadequate Nutrition

- wasting syndromes caused by malnutrition, malignant neoplasia or chronic disease (e.g. Jöhne's disease, tuberculosis) are associated with atrophy of adipose tissue and skeletal muscle and ultimately of viscera, especially the liver and exocrine pancreas but also the myocardium (Figure 3)

Figure 3



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Special Forms of Atrophy

Serous Atrophy of Fat

- an important lesion in emaciated/cachectic animals, especially the very young and very old
- with rapid mobilisation of fat stores, the normally solid, cream-white fat becomes gelatinous, translucent and often pale pink, and may shrink rapidly on exposure to air due to its high water content
- **serous atrophy of bone marrow fat** is only observed in the most advanced stages of starvation and cachexia

Small Intestinal Villous Atrophy

- villous atrophy is a common response of the small intestinal mucosa to injury
- the villi contract and become stumpy and covered by attenuated squamous, cuboidal or low columnar cells
- villous atrophy may result from:

- **increased loss of enterocytes from villi**

- e.g. due to viral, bacterial or protozal infection of the villous enterocytes
- e.g. due to transient hypoxia of the enterocytes

- **necrosis or impaired mitosis of crypt stem cells**

- e.g. due to viral injury to crypt cells
- e.g. hypoxia of greater than 2-4 hours' duration

- **dysregulation of crypt stem cell proliferation and enterocyte maturation**

- villous atrophy results from premature exfoliation of enterocytes close to the crypt openings or low on the villi
- common in chronic persistent enteritis caused by intestinal parasites, food hypersensitivity, inflammatory bowel disease, chronic bacterial infection (e.g. Jöhne's disease) and intestinal lymphoma (in which malignant lymphocytes infiltrate the mucosa +/- deeper layers of the bowel)

- irrespective of the cause, **villous atrophy → reduced intestinal absorptive area → malabsorption of nutrients** → osmotic drag of water → diarrhoea

Progressive Atrophic Rhinitis in Pigs

- affects pigs of at least 6-12 weeks of age
- caused by nasal cavity infection with toxin-producing strains of *Pasteurella multocida* (especially type D), often in concert with other bacterial pathogens (e.g. *Bordetella bronchiseptica)* `
- infection causes sneezing, nasal discharge +/- haemorrhage, nasal deformity, failure to thrive, and predisposition to secondary bacterial pneumonia (inflammation of the lungs)
- the bacterial cytotoxin causes atrophy of nasal mucus-secreting glands, resorption of nasal turbinate bones, reduced formation of new bone, and proliferation of fibroblasts with deposition of collagen
- see progressive atrophy and distortion of the nasal turbinates, and lateral deviation of the snout towards the more severely affected side

Abiotrophy

- **abiotrophy = genetically programmed, premature or accelerated degeneration of mature cell types, causing atrophy of the affected organ or tissue**

- *a = lack of, bios = vital substance, trophe = nutrition*
- presumably due to an inherited intrinsic metabolic defect in the cell population involved

- e.g. **cerebellar abiotrophy** in lambs, calves, piglets and dogs
- usually inherited as an autosomal recessive trait
- the cerebellar Purkinje cells appear to be especially vulnerable to degeneration and their demise may → secondary depletion of the cerebellocortical granule cells with which they communicate
- clinical signs of cerebellar dysfunction usually manifest at a few months of age and are progressive

- e.g. some of the **retinal photoreceptor dysplasia syndromes** in dogs that lead to **progressive retinal atrophy**
- usually inherited as an autosomal recessive trait
- characterised by progressive degeneration of retinal photoreceptors, beginning dorsolateral to the optic disc
- affected dogs may be blind by 1-2 years of age
- identified in more than 100 dog breeds (e.g. Irish setters, collies, Norwegian elkhounds, miniature schnauzers and Alaskan malamutes)
- some syndromes only affect the photoreceptor rods but most affect both the rods and cones
- in Alaskan malamutes, only the cones are affected → visual impairment only in daylight

AGEING

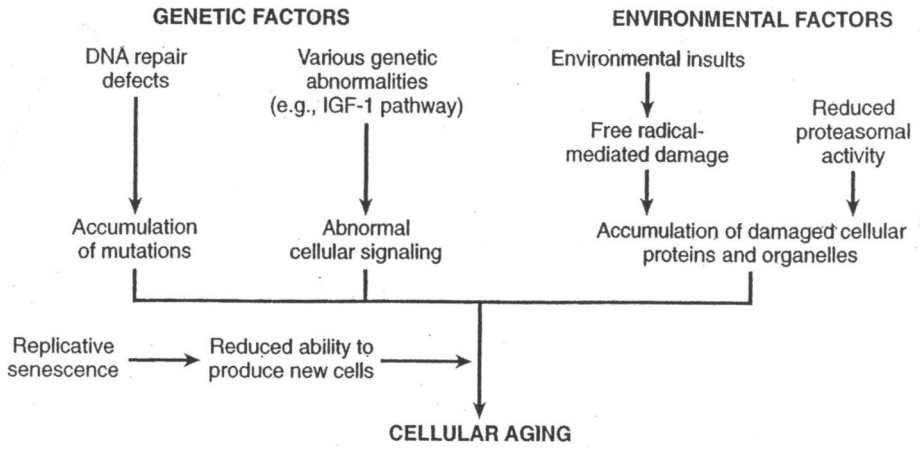
- the process of ageing involves functional and structural alterations in most organ systems
- in senility, reproductive organs undergo atrophy first, followed by muscles, fat stores, bones, lymphoid tissues and later the central nervous system

- ageing of individual animals is influenced by genetic factors, nutritional quality, husbandry factors, and by the occurrence of age-related diseases (e.g. renal failure, neoplasia, degenerative joint disease, osteoporosis, dental disease)
- decreases in nutrient intake, blood supply, hormonal stimulation and workload, and impaired immune function probably contribute to ageing of organisms

- **ageing of cells is an important component of ageing of organisms**
- the pathogenesis of cellular ageing is incompletely understood but the process appears to be **multifactorial** (Figure 4)
- cellular ageing involves a progressive decline in the replicative capacity and intrinsic lifespan of the cell and the accumulation of cellular and molecular damage caused by intrinsic and extrinsic “wear and tear” factors to which the cell has been exposed throughout its life

- smaller animals tend to have a higher metabolic rate and usually a shorter life span than larger animals
- the reduction in lifespan probably reflects accumulation of greater injury to cellular organelles and molecules caused by the higher rate of metabolism throughout life

Figure 4



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Functional and Structural Deterioration of Aged Cells

- structural changes that may be observed in aged cells include an irregular nuclear shape (including abnormal nuclear lobation), vacuolation of mitochondria, decreased endoplasmic reticulum, distortion of the Golgi apparatus, and accumulation of lipofuscin in cytoplasmic residual bodies

- the structural changes are accompanied by a functional decline
- e.g. reduction in mitochondrial oxidative phosphorylation
- e.g. reduction in synthesis of nucleic acids, structural and enzymatic proteins, cell receptors and transcription factors
- e.g. decreased repair of chromosomal damage
- e.g. decreased cell uptake of nutrients

Replicative Senescence

- after a fixed number of mitotic divisions, all cells become arrested in a terminally non-dividing state (= **cellular senescence**)
- the number of mitotic divisions permitted throughout life varies with the cell type

- **telomere shortening** may explain the fixed lifespan of somatic cells
- telomeres are short repeated sequences of DNA (TTAGGG) located at the ends of chromosomes
- they ensure complete replication of chromosome ends during mitotic division and protect the ends of chromosomes from fusion or degradation
- with each mitotic division, a small part of each telomere is not duplicated
- progressive telomere shortening can be prevented by addition of new nucleotides, mediated by the enzyme **telomerase**
- telomerase activity is expressed in germ cells and at low levels in stem cells but not in most somatic cells
- progressive telomere shortening in somatic cells eventually leads to an inability of these cells to undergo mitotic division and hence replace lost or damaged cells

Accumulation of Cellular and Molecular Injury

- normal cellular metabolism generates **reactive oxygen species** (**ROS**, **free radicals**) as by-products of oxidative phosphorylation
- ROS can lead to oxidative injury to and covalent modification of cell nucleic acids, proteins and lipids
- these injuries are cumulative throughout the lifespan of the cell
- cellular injury caused by ROS can be magnified if anti-oxidant defences are reduced (e.g. depletion of vitamin E or reduced glutathione) or there is tissue injury (e.g. ROS are generated during inflammatory processes)

- aged cells accumulate **advanced glycation end products** that result from non-enzymatic glycosylation reactions → cross-linking of adjacent proteins and accumulation of abnormally folded proteins
- **proteasome function** also declines with cell age, allowing these abnormal proteins to persist
- e.g. age-related glycosylation of lens proteins → **senile cataracts** with lens opacity

- the capacity of **endogenous DNA repair enzymes** to recognise and repair damaged DNA segments also declines with cell age → accumulation of mutations → impaired cell function

How to Prevent Ageing

- experimentally, the most effective means to prolong the lifespan of animals is **caloric restriction**
- thought to be mediated via promotion of the activity of **sirtuins** (**Sir2 proteins**), a family of proteins with either mono-ADP-ribosyltransferase or deacylase activity
- sirtuins → increased production of proteins that reduce apoptosis
  → stimulation of protein folding
  → increased metabolic activity and insulin sensitivity
  → decreased generation of ROS

- in several mutant mouse models, impairment of the axis between growth hormone (GH) and insulin-like growth factor 1 (IGF-1) receptors → prolongation of lifespan (and also increased insulin sensitivity but the latter is NOT necessary for prolongation of the lifespan)