**Progressive changes**

**Progressive changes** (*metamorphoses progressivae)* is a branch of general pathology, which examines adaptive changes of cells and tissues in response to sub-lethal damage (oxidative stress, damaging factors) or increased demand for the work of a given tissue.

Progressive changes consist mainly of:

* an increase in the number of cells ***(hyperplasia)***
* increased production of cell organelles leading to the increase in the cell size (***hypertrophy***)

If these processes are not fully supervised by the body control mechanisms, they can be a starting point for pre-neoplastic or neoplastic proliferation.

Progressive changes are characterized by increased activity of vital cells or tissues of the animal body, as a result of which the processes of synthesis (assimilation) prevail over the processes of disintegration (assimilation).

Progressive changes include:

* regeneration (*regeneratio)*
* repair (*reparatio)*
* hypertrophy (*hypertrophia)*
* hyperplasia (*hyperplasia)*
* metaplasia and transformation (*metaplasia et transformatio)*
* non-neoplastic tumours (*noduli non neoplasmaticae)*

**Hyperplasia** - is an increase in the number of cells (increase in mitotic activity), which results in an increase in the size of the tissue, the organ or its parts.

Microscopically, the cells are similar to normal cells, but their number is higher. Cells that have been affected by hyperplasia may also be of increased size, which means that they have been at the same time affected by hypertrophy (*hypertrophia*).

Hypertrophy and hyperplasia are closely related and often occur simultaneously, contributing to the overall enlargement of the organ, e.g. in the pregnant uterus.

Hyperplasia can be:

* physiological
  + **hormonal -** proliferation of lactic epithelial cells before lactation, pregnant uterus
  + **compensatory -** tissue regeneration after its partial removal or damage, stimulated by growth factors produced by organ cells and interstitial connective tissue
  + pathological **-** primarily caused by excessive stimulation by hormones or growth factors (cystic endometrial hyperplasia in bitches as a result of prolonged exposure to progesterone; nodular hyperplasia of the spleen, liver or pancreas in old dogs)

**Cystic endometrial hyperplasia:**

Microscopically:

* increase in the number of cells in glands
* excessive secretion of glands
* cyst formation

***Splenic nodular hyperplasia***- a progressive non-neoplastic lesion, common in older dogs, involves chaotic proliferation of:

* white pulp elements (splenic nodule proliferation centres, marginal zone and T-zone lymphocytes)
* red pulp
* blood cell precursors (extramedullary hematopoiesis)

It may contain one, two or three of the above elements (complex type).

**Mammary gland fibrosis (*fibrosis mammae*)** **-** the proliferation of fibrous tissue within the mammary gland, initially the connective tissue is hypercellular, then the cells produce the intercellular substance and the collagen fibres that become hyalinized - which contributes to the hardening of the gland (mammary gland sclerosis *sclerosis mammae).*

As a result of the pressure of the growing connective tissue on the adjacent cells, glandular tissue (the pulp of the organ) disappears.

**Hypertrophy (*hypertrophia*)** *-* consists of an increase of the mass or volume of cells, while the total number of cells in the organ remains constant. Cellular enlargement is the result of an increase in the synthesis of cellular organelles (either physiological or pathological) and may be caused by an increased functional demand (intensive work, training, compensatory growth, after removal of part of the organ) or specific hormonal stimulation.

Hypertrophy can occur in various organs and tissues, but usually involves cells with low proliferative potential. It is quite common in striated muscles.

**Causes**:

* growth factors
* hormones (uterine muscle hypertrophy - oestrogens)
* mechanical stress (skeletal muscle hypertrophy)
* medicines
* activation of specific genes

Physiological hypertrophy - of skeletal muscle fibres as a result of intensive training

Compensatory hypertrophy - hypertrophy of the remaining kidney after the loss of the other one (initially hypertrophy, then hyperplasia of the cells, increase in the length of nephrons); right ventricular hypertrophy due to, for example, failure of the pulmonary artery valve or pulmonic stenosis.

At the cellular level, the increase in organelle size and their arrangement reflects the work in which the cell is involved. For example, long-term exposure to various substances, e.g. Phenobarbital, Dilantin (phenytoin), alcohol, leads to an enlargement of the smooth endoplasmic reticulum in hepatocytes, as SER contains a system of oxidative enzymes responsible for catabolism of these compounds. On the other hand, an increase in Golgi complex size and rough endoplasmic reticulum in the cell reflects the demand for the synthesis of extracellular proteins (immunoglobulin, collagen). Mitochondrial hypertrophy is the result of cellular demand for ATP. An increase in nucleolar size and the euchromatine ratio reflects the activity of synthesis processes in the cell.

**Benign prostatic hyperplasia (*hypertrophia prostatae)*** in dogs

Prostatic hyperplasia usually occurs together with cellular hyperplasia and develops spontaneously with age or as a result of hormonal disorders (an increase in androgens and oestrogens or an increase in the number of receptors on the glandular cells).

**Repair (*reparatio)*** *-* occurs when a tissue with little or no regenerative capacity is damaged or when the size of the loss exceeds this capacity. The loss is then filled with young connective tissue - granulation tissue ***(granulatio),*** with a dense network of blood capillary capillaries. The repair process consists of three phases:

**Phase 1** - blood extravasation and clot formation, chemotaxis (inflammatory mediators) of granulocytes (48 hours) and macrophages; removal of dead tissues; mobilization of fibroblasts and endothelial cells - this is the superficial (youngest) layer of granulation tissue.

**Phase 2** - proliferation of fibroblasts, myofibroblasts and endothelial cells; endothelial cells are arranged in strands forming the beginnings of blood vessels, which gradually gain vascular lumen and by joining together form a new vascular channel; loose connective tissue rich in vessels, fibroblasts and the ground substance is formed - this is the middle (medium) layer of granulation tissue.

**Phase 3** - gradual disappearance of blood vessels, the number of fibroblasts, myofibroblasts decreases, the number of collagen fibres increases with their subsequent shrinking - this is the deepest (oldest) layer of granulation tissue. Over time, the connective tissue becomes fibrous, hard, leading to scar formation **(*cicatrix*)***.* An excess of granulation tissue growth, which sometimes occurs in skin, is called proud flesh **(*caro luxurians*)***.*

**Metaplasia (*metaplasia*)**

* is the replacement of one mature cell types with another mature cell type of the same origin
* usually highly specialised cells, e.g. epithelial, are replaced by less specialised epithelial cells
* new cells come from lowly differentiated stem tissue cells
* metaplasia is usually a reversible process provided that its causative factor is removed; otherwise it may be the starting point for neoplastic hyperplasia

An example of epithelial metaplasia includes:

* the appearance of multi-layered squamous epithelium **(squamous metaplasia)** in place of respiratory epithelium (ciliated columnar epithelium) in heavy smokers. The newly emerging epithelium is more resistant to damage; however, due to the absence of cilia and mucus production, it has a lower protective effect on the lung tissue
* replacement of the normal stratified squamous epithelium in the distal oesophagus with columnar epithelium, typical of the stomach or intestines in case of chronic gastroesophageal reflux

Metaplasia can occur in tissues of mesenchymal origin.Adaptive changes are less frequent, usually in response to changes in the cell environment, e.g. oxygen concentration, and bone or cartilage tissue can appear in areas of soft tissue damage (chronic inflammation, tumours - often of the mammary gland).

**Causes of tissue metaplasia:**

* chronic irritation by chemical or physical agents
* chronic inflammation, presence of stones in the duct lumen (squamous metaplasia in salivary glands, biliary and pancreatic ducts)
* long exposure to hormones, e.g. oestrogens, causes the formation of squamous epithelium, keratinizing and exfoliating in the urinary tract and prostate;
* damage to or failure of the bone marrow may cause myeloid metaplasia (extramedullary hematopoiesis) in the mature spleen or liver;
* vitamin A deficiency (squamous metaplasia of the transitional epithelium of the urinary tract or the epithelium of the mucous glands of oesophageal mucosa in birds)
* osseous metaplasia in areas of injured connective tissue

**Squamous metaplasia** may appear in the bladder as a result of chronic inflammation, schistosomiasis, diverticulum or neurogenic disorders. The appearance of stratified keratinized epithelium may become the site of growth of cancer (mainly keratinising carcinoma) and other complications such as, for example, bladder contracture or blockage.

**Squamous metaplasia (keratinising metaplasia)** of the prostate in dogs is the result of hyperestrogenism (hyperestrogenism usually results from the presence of a hormonally active testicular tumour - usually sertolioma);

* grossly: the gland is enlarged
* in the microscopic preparation, the replacement of the normal glandular epithelium with stratified epithelium can be observed, sometimes with pronounced keratosis
* squamousmetaplasia may be accompanied by glandular stromal proliferation and inflammation

**Squamous metaplasia**

* may also result from chronic irritation, e.g. nasal epithelium in brachycephalic dogs, respiratory epithelium in smokers
* it is also sometimes found within the epithelium covering mucous membrane polyps, e.g. gastric polyps

**Gastric intestinal metaplasia** consists of:

* transformation of gastric epithelium into the intestinal type with the presence of goblet cells
* atrophy of gastric mucous membrane elements
* primitive glands and intestinal villi (pseudo-villi) emerge in place of the glands
* newly emerged glands do not function as gastric glands - they do not produce gastric juice
* inflammatory cell infiltration is observed in the in lamina propria, especially when the cause of metaplasia is chronic gastritis (atrophic gastritis in the course of Helicobacter pylori infection or as an autoimmune disease)
* the newly formed epithelium tends promote neoplastic transformation
* it can occur in different areas of the mucosa, usually has a focal nature

**Myeloid metaplasia (extramedullary hematopoiesis)**

* most often occurs in the spleen, rarely in the liver or lymph nodes;
* may result from damage to the bone marrow, chronic hypoxia or increased blood cell turnover, e.g. in haemolytic anaemia or in chronic bleeding (e.g. on the edges of extensive spleen haematomas)
* **grossly:** the spleen can be evenly enlarged
* **microscopically:** multifocal or diffuse proliferation of blood cell precursors of different hematopoietic lines - erythrocyte, myeloid and megakaryocyte lines - is observed.

**Dysplasia (*dysplasia*)** is a process involving the emergence of cells with an abnormal appearance and leading to a change in organ architecture. It is a reversible process when the etiological factors cease to operate. The most common causes include:

* hormonal imbalance
* chronic inflammation
* dietary errors
* prolonged tissue irritation

Dysplasia is mainly characterized by microscopic changes:

* ***anisocytosis*** - the cells of the same tissue have different sizes
* ***poikilocytosis*** - non-standard cell shapes
* ***macrocytosis*** - cell size increase
* ***hyperchromatosis*** – nuclear hyperpigmentation (increase in DNA amount)
* ***macronucleosis*** - enlarged nucleus
* ***polynucleosis*** - presence of multiple nuclei within a given cell
* ***vacuolisation*** - emergence of an increased number of vacuoles in cells
* the presence of many figures of mitotic divisions (atypical number of cells dividing at the given moment)

The degree of severity and extent of changes within the cells and tissues provides the basis to determine low-, medium- and high-grade dysplasia. The higher the grade of dysplasia, the greater the probability of a neoplastic transformation.

**Mammary gland dysplasia (*dysplasia mammae*)**consists of disorders of the proliferation of epithelial components and connective tissue stroma, as a result of an imbalance between oestrogens and progesterone in favour of progesterone. The changes are characterized by blurred, delimited foci of increased pulp consistency. They occur unilaterally or bilaterally.

The histological picture depends on the severity of proliferative and atrophic changes, both within the parenchyma and the stroma. The following are observed:

* proliferation of the mammary duct epithelium**(*epithelioplasia/epitheliosis)***
* duct extension **(*ectasia ductum*)**
* cysts **(*cystes*)**emerging as a result of a significant extension of the ducts
* proliferation of the mammary gland epithelium **(*adenoplasia*)**
* **adenosis** characterised by the diffuse proliferation of small ducts and stroma fibrosis
* fibrosis or hardening of the mammary gland **(*fibrosis et sclerosis mammae*)**

Dysplasia can be accompanied by neoplastic changes, in particular in cases of simultaneous occurrence of mixed tumours in beaches.

**Fibroadenomatous change -** proliferation of glandular ductules and ducts, surrounded by abundant, proliferating, loose connective tissue stroma.

**Non-neoplastic tumours** **(*noduli non neoplasmaticae*)**

A **Cyst (*cystis*)** is a cavitary formation, filled with homogeneous masses of abnormal keratin, serous fluid, protein fluid, residual hair, exfoliated cells, erythrocytes, etc. When its wall is made of epithelium consisting of one or more layers of cells, surrounded by a layer of connective tissue, it is a true cyst**(*cystis vera*)**; if it has no epithelial lining it is called a pseudocyst **(*cystis* *spuria****,* ***pseudocystis*)**.

**True cysts** often occur in the skin of dogs and cats as a result of clogged glandular ducts or are formed from hair follicles (epidermoid cysts) as a result of injuries or inborn predispositions.

**Pseudocysts** can occur in different organs as a result of trauma or haemorrhage, e.g. in the brain after a infarction or stroke, or within tumours.

**Neoplasms, part 1**

**Neoplasm** (***neoplasma*)** *-* is an abnormal, uncontrolled, continuous growth of tissue, occurring faster than the surrounding healthy tissue.

Neoplastic cells differ from normal cells in:

* uncontrolled multiplication, inadequate to the requirement of the body
* cellular differentiation disorders
* disturbance of communication between cells and adhesion to the substrate.

Each neoplasm has its Latin name in the neuter gender, ending with ***– oma*** e.g.fibroma, and in plural it takes the ending ***– ata,*** e.g. fibromata.

Neoplasms can originate from different tissues. Generally, they are divided into:

* benign tumours **(*neoplasma benignum)***
* locally malignant and malignant neoplasms **(*neoplasma malignum*)**

CARCINOMAS ***CARCINOMA*** *-* of epithelial origin

SARCOMAS ***SARCOMA*** *-* of mesenchymal origin

Every neoplasm consists of

* ***parenchyma* -** actual proliferating neoplastic cells
* ***stroma*** - connective tissue surrounding neoplastic cells, tumour-associated cells, e.g. inflammatory cells

**Classification of mesenchymal neoplasms**

1. Neoplasms of fibrous tissue

* benign: fibroma, myxoma
* locally malignant: sarcoid
* malignant: fibrosarcoma, myxosarcoma

1. Adipose tissue neoplasms

* benign: lipoma, infiltrative lipoma, angiolipoma
* malignant: liposarcoma

1. Smooth muscle neoplasms

* benign: leiomyoma
* malignant: leiomyosarcoma

1. Striated muscle neoplasms

* benign: rhabdomyoma
* malignant: rhabdomyosarcoma

1. Vascular neoplasms

* benign: hemangioma, lymphangioma
* malignant: hemangiosarcoma, lymphangiosarcoma

1. Peripheral nerve sheath neoplasms

* benign: granular cell tumour, schwannoma
* malignant: malignant schwannoma

1. Synovial membrane neoplasms

* malignant: synovial cell sarcoma

1. Mesothelial neoplasms

* indirect malignancy: mesothelioma

1. Unclassified neoplasms

* malignant: hemangiopericytoma, malignant mesenchymoma

1. Bone and joint neoplasms

* benign: chondroma, osteoma
* malignant: chondrosarcoma, osteosarcoma

**Characteristics of benign neoplasms**

|  |  |
| --- | --- |
| Growth rate | Slow (many years) |
| Encapsulation | Usually, there is a clear boundary between healthy tissue and neoplastic tissue |
| Growth type | * Expansive (they grow by expansion, pressing against the surrounding tissue) * No infiltration of healthy tissues |
| Post-operative recurrence | None |
| Penetration into vessels | None |
| Metastases | None |
| Histological structure | * Well-differentiated cells, morphologically similar to mature cells of the tissue from which they originate * Disturbance of the cellular arrangement in relation to the tumour and the stroma as compared to normal tissue - disorganised tissue architecture * Rare, usually normal mitotic figures |
| Effects on the body | Often intangible; dangerous when located in an important organ such as the brain |
| Regressive changes | Rarely (degenerations) |

**Fibroma**

* a benign, well-diversified neoplasm, derived from fibrous tissue cells (fibroblasts)
* occurrence: skin, subcutaneous tissue, mucous membranes (e.g. oral mucosa)
* tumours of various consistencies (often quite hard), pedunculated or not, clearly encapsulated
* neoplastic parenchyma: neoplastic fibrocytes, fibroblasts chaotically arranged, in different directions, forming characteristic whirls and tissue streaks, spindle-shaped, with elongated nuclei, usually with pointed ends
* stroma: collagen, reticulin and elastic fibres

Fibroma types:

* **Hard fibroma (*fibroma durum*)**-grows in the form of well-delimited hard tumours, stroma made of numerous fibroblasts and densely compacted collagen fibres. Fibrocytes have elongated, spindle-shaped or oval hyperchromatic nuclei. Mitotic figures are absent or rare. Collagen fibres run in different planes, which gives an image of whirls, or they run in parallel lines.
* **Soft fibroma (*fibroma molle*)** - is a well-delimited, white-grey, flexible, soft tumour, wet and viscous on the surface of its cross-section. Histologically, neoplastic fibroblasts and fibrocytes are spindle-shaped and elongated, can often take a star-like shape and are surrounded by the ground substance of the connective tissue stroma, with the presence of reticulin fibres (mainly type III collagen), adipocytes and even interstitial lipid deposits.

**Myxoma**

* benign, well-diversified neoplasm
* loose-textured
* it originates from connective tissue cells - fibroblasts or from multipotential mesenchymal cells
* neoplastic cells are few, spider-shaped, star-shaped or spindle-shaped, with a small hyperchromatic nucleus, mitotic figures are rare
* cells are connected to each other by means of long, filamentous processes, forming a grid, which includes few tiny collagen fibres of the connective tissue with blood vessels; mucosal masses - mainly glycosaminoglycans - accumulate around the cells
* it grows in the form of single, soft or jelly-like, grey, yellow-pink tumours, usually unencapsulated, often infiltrating the surrounding tissues, and is usually located in the skin, subcutaneous tissue and mucous membranes
* on the cross-section, the neoplastic parenchyma is pale, with the presence of a viscous fluid
* recurrence after surgical resection is common due to the infiltrating growth of the neoplasm

**Chondroma**

* originates from hyaline cartilage, less frequently from fibrocartilage
* neoplastic chondrocytes and chondroblasts are located in irregularly arranged cavities (usually two or more in each)
* chondroma cells are of different sizes **(*anisocytosis*)***,* may take different shapes (oval, spherical, elongated) and may be multinucleated
* neoplastic parenchyma is generally abundant and poorly vascularised and may undergo processes of calcification or ossification
* chondroma is rare in animals, usually these are hard, spherical, smooth or nodular tumours, whitish on the cross-section, with a relatively thin connective tissue capsule or without it
* chondroma originally growing out of the bone marrow cavity - enchondroma, and growing out of cartilage on the surface of the bone - ecchondroma

**Lipoma**

* benign neoplasm derived from adipose tissue cells
* lipomas grow slowly, often reaching a large size, are well demarcated and covered with a thin connective tissue capsule
* occur in mature and old animals - average age: about 8 years
* in dogs, they are often located in the subcutaneous tissue of the area of chest, abdomen, limbs, between the muscles; in horses, it often occurs in the pedunculated form in the mesoileum, contributing to intestinal torsion, which can cause the death of the animal
* neoplastic cells resemble normal adipocytes, are of different sizes, often large, sometimes multinucleated (lipoblast-like), with immature cytoplasmic lipid droplets
* the tumour stroma is formed of fibrous tissue in which blood vessels are present; it often divides the neoplasm into lobules of different sizes

**Neoplastic growth of adipocytes may be accompanied by the proliferation of other cell populations:**

* fibroblast proliferation – fibrolipoma
* vascular proliferation – angiolipoma
* chondrocyte proliferation - chondrolipoma