**Inflammation, part 1**

Inflammation **(**from Latin: ***inflammatio*)** is a complexprotective response of the immune system and the connective tissue to the following noxious factors:

* physical
	+ mechanical
	+ thermal
	+ radiation
* biological
	+ exogenous: bacteria, viruses, fungi, insects
	+ endogenous: necrotic tissues, neoplasms, autoantigens, immune complexes
* chemical
	+ exogenic: alcohol, medications, heavy metals
	+ endogenic: urea, uric acid, pancreatic lipase.

**The primary symptoms include:**

* ***rubor*** – redness
* ***tumor*** – oedema
* ***dolor***- pain
* ***calor***– increased temperature
* ***functio laesa*** – loss of function.

**The purposes of inflammation:**

* elimination of foreign substances
* restoration of the physiological functions of the organs and tissues **(*restitutio ad integrum*)**
* repair or regeneration of the affected tissue **(*reparatio*)**with the development of the granulation tissue and scar formation*.*

The inflammation pathway is determined by a variety of factors called mediators or modulators of inflammation developing in response to the ongoing immune reaction, both humoral and cellular.

**The mediators of inflammation are developing from:**

* bacteria
* injured tissues
* basal cells
* leukocytes
* the cascade of complement degradation.

The mediators of inflammation affect the ongoing inflammatory process by **feedback loops.**

**Stages of Inflammation**

1. The vascular stage is triggered immediately after tissue damage, and following momentary ischaemia, the blood vessels are dilatating.
2. The exudation stage involves the accumulation of fluids in the extravascular space and the development of oedema.
3. The cellular stage involves leukocyte migration towards the site of inflammation.

Monocyte:

* is produced in the bone marrow
* enters the bloodstream
* initiates the development of macrophage population in tissues
* has a kidney-shaped or oval nucleus.

Histiocytes (macrophages and dendritic cells)

* a heterogeneous population
* found in:
	+ splenic pulp
	+ bone marrow
	+ liver
	+ lungs
	+ body cavities (pleural and peritoneal)
	+ skin
* the population includes:
	+ resident cutaneous macrophages
	+ antigen-presenting dendritic cells
	+ osteoclasts
	+ microglia
	+ exudative macrophages

Their main function involves **phagocytosis** (non-specific and immune phagocytosis) and digestion of the phagocytised material. Numerous macrophages fuse and produce **multi-nucleated giant cells**.

Mast cell (mastocyte, labrocyte)

* is produced in the bone marrow and from there, it migrates and enters the target tissues, initiating the development of a mast cell population
* cytoplasmatic granules (basophilic) containing the following mediators of inflammation:
	+ heparin
	+ histamine
	+ serotonin
	+ dopamine
	+ Zn2+ ions
	+ SRS-A (Slow Reacting Substance of Anaphylaxis is a mediator of type 1 hypersensitivity)
	+ numerous chemotactic agents that are responsible for the inflow of inflammatory cells (such as neutrophils) to the site of a disease process
	+ mediators of inflammation involved in the immune responses (immediate and delayed hypersensitivity).

**Granulocytes**

Eosinophils

* have acidophilic cytoplasmatic granules
* can “kill” parasites (oxidation process with peroxidase)
* capacity for phagocytosis (mainly the antigen-antibody complexes)
* excrete bactericidal compounds
* detected in:
	+ allergic diseases
	+ parasitic diseases
	+ some malignant neoplastic diseases (e.g. mast cell tumour, anal sacs adenocarcinoma).

Neutrophils

* contain azurophilic granules in the cytoplasm
* young neutrophils have a band-shaped nucleus
* older cells have a segmented nucleus (2-5)
* excrete the mediators of inflammation and bactericidal agents
* in tissues, they behave like macrophages (phagocytize bacteria) and have a lifespan of 1-2 days.

Basophils

* contains acidophilic granules in the cytoplasm
* produce the mediators of inflammation and some bactericidal agents
* have a capacity for phagocytosis
* are involved in inflammatory and allergic reactions.

**Lymphocytes**

* B cells are involved in the humoral immune response:
	+ produce specific antibodies
* T cells are involved in the cellular immune mechanisms:
	+ Tc: cytotoxic T cells (e.g. destroy cells infected with viruses, neoplastic cells)
	+ Th: helper T cells (activate B cells, the other T cell types, and different cells)
	+ Ts: suppressor T cells (inhibit the immune response and trigger a signal to terminate the mechanism)
* Null T cells without markers, including:
	+ K (killer) cells are responsible for antibody-dependent cytotoxicity
	+ NK (natural killer) cells spontaneously destroy the virus-infected cells, young cells and adolescent cells, as well as intensively dividing cells (neoplastic cells).

Plasma cells

A mature form of the B cell found in abundant amounts in the connective tissue near the sites exposed to antigens or during inflammatory reactions. Its main function involves synthesizing immunoglobulins. The nuclei of plasma cells are round, with a specific cartwheel arrangement of chromatin and usually located at the periphery of a cell.

The “Mott” cell is an active plasma cell that contains the so-called Russel bodies in the cytoplasm; these are immunoglobulins found in the vehicularly expanded rough reticuloendothelial system (RER).

**Terminology of Inflammation**

The radix originates most commonly from the Greek name of an organ. For example:

METRA-itis

* endo-metr-itis
* myo-metr-itis
* peri-metr-itis
* para-metr-itis

**Note!**

***Pneumonia – Inflammation of the lungs***

**Morphological Classification of Inflammation**

Each inflammatory process demonstrates the signs of disturbances in circulations (hyperaemia, extravasations, exudation), regressive changes (degeneration, necrosis) and proliferative changes (hyperplasia and hypertrophy). Depending on the predominance of the specific lesions over the other ones, three types of inflammation are discussed:

* altering inflammation **(*inflammatio alterativa*)**is most common in the parenchymatous organs: parenchymatous inflammation **(*infammatio parenchymatosa*)**
	+ damage **(*alteratio*)** – degeneration/necrosis **(*degeneratio/necrosis*)**
	+ restoration **(*restitutio ad integrum*)**
	+ fibrosis **(*fibrosis*)**
* exudative inflammation **(*inflammatio exsudativa*)** is most often found in the tissues with the epidermal layer
	+ exudation/exudate **(*exsudatio/exsudatum*)**
		- serous inflammation **(*inflammatio serosa*)**
		- fibrinous/croupous inflammation **(*inflammatio fibrinosa/crouposa*)**
		- purulent inflammation **(*inflammatio purulenta*)**
		- catarrhal inflammation **(*inflammatio catarrhalis*)**
		- haemorrhagic inflammation **(*inflammatio haemorrhagica*)**
		- gangrenous inflammation **(*inflammatio gangraenosa/ichorosa)***
* proliferative inflammation **(*inflammatio productiva s. proliferativa*)** most commonly affects the epidermis and interstitial connective tissue
	+ acute **(*acuta*)** with inflammatory infiltrate and minor proliferation of the interstitial tissue cells
	+ chronic **(*chronica*)** with inflammatory infiltrate and proliferation of the cells and tissues (epidermal or connective tissue); development of cirrhosis **(*cirrhosis*)**and granulomas **(*granuloma*).**

**Exudative inflammation (*inflammationes exsudativa*)**

Serous inflammation**(*inflammatio serosa*)**develops in response to a non-potent inflammatory stimulus and may cease without any consequences or progress into a different type of exudative inflammation. It can affect any organ (lungs, mucosa, serosa, liver). During this pathological process, the blood vessels become mildly damaged, with serum leakage and the development of exudate.

Serous exudate is:

* a clear fluid with more than 4% protein content:
	+ albumins
	+ globulins
	+ traces of fibrin
	+ cellular component: single neutrophils, lymphocytes, monocytes and exfoliated epidermis.

Serous exudate can undergo:

* resorption
* and if the exudate persists, it triggers proliferation of the connective tissue with resulting clumping **(*adhesiones*)**and adhesions **(*accretiones*).**

Types of the exudate:

* free exudate **(*exsudatum liberum***): serosa, body cavities, alveoli, mucosa
* tissue-infiltrating exudate**(*infiltratum*)**
* penetration of inflammatory exudate to the cells with resulting cell damage, e.g. in hepatic cells **(*insudatum***).

**Serous pneumonia (*bronchopneumonia serosa*)**

Grossly: inflammatory sites in the lungs are non-aerated, enlarged, swollen, with red, blue-red, brown-red colour and solid texture. The cut surface is smooth, moist, with foaming fluid effusing on the cross-section.

Microscopically: hyperaemia, serous exudate in the alveoli and interstitium, slight thickening of the alveolar walls and peribronchial tissue, and leukocyte infiltrates. If the alveolar lumen contains numerous desquamated pneumocytes, the pathology is called desquamative pneumonia **(*bronchopneumonia desquamativa*)**.

**Catarrhal inflammation (*inflammatio catarrhalis*)**

It is distinguished by seromucous exudate and affects the mucosal layers and the lungs. Transient inflammation does not bring about any morphological after-effects while a long-lasting inflammatory process and accumulation of the seromucous exudate cause proliferation of the connective tissue, with resulting induration of the organ.

Catarrhal exudate **(*catarrhus*)** consists of:

* serous exudate
* mucous produced in an excessive amount by the goblet cells and mucous glands
* exfoliated epidermis and the debris of damaged tissues
* small debris of coagulated blood
* fibrin strands
* single neutrophils, lymphocytes, and erythrocytes.

**Catarrhal pneumonia (*bronchopneumonia catarrhalis*)**

This pathology is most often located in the least aerated lung lobes (cranial and cardiac). The inflammation begins in the bronchioles and expands onto the associated alveoli or peribronchial zone, involving the peribronchial tissue and neighbouring lymphatic vessels. The inflammatory exudate accumulating in the affected area fills the alveolar lumen, and the air contained in the alveoli networked with the diseased alveoli is reabsorbed, which makes the pulmonary tissue to collapse (atelectasis). The inflammatory process expands over the atelectatic lung tissue, and thus, the inflammatory foci are usually disseminated in the lung tissue, of different sizes, and include the single lobules or the groups thereof.

Grossly: the foci of inflammation are slightly elevated over the lung surface, red, livid red or brown-red, non-aerated, consolidated; on the cross-section, shining and moist, effused with light grey or brown-red, turbid and slightly foamy fluid.

Microscopically: seromucous exudate in the alveoli and bronchioles is highly cellular (single neutrophils, macrophages, lymphocytes, erythrocytes, and desquamated epidermis). Furthermore, hyperaemia and swelling of the alveolar walls are reported. Compensating emphysema develops in the lung zones not affected by the inflammation. When the inflammatory process persists, the proliferation of the connective tissue and pulmonary fibrosis (hardening) are discussed.

**Catarrhal gastritis(*gastritis catarrhalis*)**

**Acute catarrhal gastritis** **(*gastritis catarrhalis acuta*)**

Grossly: the gastric mucosa with diffuse or spotted hyperaemia, softened and lined with abundant amounts of seromucous exudate; sometimes with extravasations and erosions **(*erosiones*)**.

Microscopically: hyperaemic gastric mucosa, inflammation, cellular infiltrates, copious amounts of mucus on the gastric lining.

**Chronic catarrhal gastritis(*gastritis catarrhalis chronica*)**

The pathology originates from the acute inflammations or develops as a primary chronic inflammatory process due to the disturbances of circulation in the stomach **(*gastritis venostatica*)**or irritating effects of the ingested or excreted substances **(*gastritis excretoria*).**

1. **Hypertrophic type** **(*gastritis catarrhalis chronica hypertrophicans*)**

Grossly: the gastric mucosa is focally or diffusely thickened, grey, livid red, folded and lined with turbid and rubbery mucous.

Microscopically: profuse cellular infiltrates (with lymphocytes and plasma cells) encompassing the whole mucosal layer and tunica muscularis of the gastric mucosa; the proliferation of the connective tissue; hypertrophic gastric glands demonstrated by the papillary or polyp-like thickenings in the mucosal layer **(*gastritis polyposa*)**; when the glandular ducts become obstructed, retention cysts develop. The gastric glands may become atrophic and replaced by the intestinal-like glands (intestinal metaplasia). Furthermore, the following lesions are discussed:

* sites of lymphadenoplasia
* erosions
* intraepidermal micro-abscesses.
1. **Atrophic type (*gastritis catarrhalis chronica atrophicans*)**

Grossly: the gastric mucosa is thin, grey, and lined with abundant amounts of mucus.

Microscopically: progressive atrophy of the mucosa (glandular and stromal structures)

**Fibrinous inflammation** **(*inflammatio fibrinosa s. inflammatio crouposa*)**

It develops when the vascular barrier is severely damaged and fibrinogen escapes from the blood vessels, where it is transformed into fibrin. Initially, the pathological process is serofibrinous inflammation. Fibrin accumulates in:

* serosa
* mucosa
* lungs (alveolar lumen)
* synovial membranes
* deep in the tissues/near the blood vessels, then it is fibrinous inflammations.

Fibrinous exudate is composed of:

* serous fluid
* fibrinogen which is transformed into fibrin
* flaked cells, neutrophils (responsible for white colour), and macrophages
* fibrin agglomerates can be dissolved by the granulocytic enzymes and plasmin and then absorbed, or they can be organized, which results in clumping and adhesions.

Types of fibrinous inflammation

* superficial**(*inflammatio superficialis*)**
* deep **(*inflammatio profunda*)**
	+ pseudomembranous **(inflammatio *pseudomembranacea s. inflammatio diphteroides*)**
	+ crusting **(*inflammatio escharotica*).**

**Croupous pneumonia(*bronchopneumonia crouposa s. bronchopneumonia fibrinosa*)**

This type of inflammation is caused mostly by Pasteurella, mycoplasma, pneumococci and streptococci. It expands intrabronchially and peribronchially. Its major feature is a phase-like course:

* infiltration stage **(*stadium infiltrationis*)**
	+ grossly: the lungs are enlarged, heavy, dark red and aerated
	+ microscopically: dilatation and hyperaemia of the alveolar septa, small amounts of exudate in the alveoli, a fine fibrin mesh near the walls, single erythrocytes, macrophages, and neutrophils
* hepatization stage **(*stadium hepatisationis*)**
	+ red hepatization **(*hepatisatio rubra*)**
		- grossly: the lungs are enlarged, heavy, red-grey, with a solid texture resembling the liver, non-aerated, and dry on the cross-section.
		- microscopically: fine fibrin strands are found in the alveolar lumen; they are arranged in a mesh with embedded numerous erythrocytes and less common neutrophils, macrophages, and desquamated epidermis; severe hyperaemia of the alveoli septa is still reported
* rusty hepatization **(*hepatisatio fusca*)**
	+ - grossly: the lungs are rusty, non-aerated and solid
		- microscopically: degradation of the erythrocytes and accumulation of large amounts of hemosiderin
* grey hepatization **(*hepatisatio grisea*)**– disease exacerbation, the highest mortality
	+ - grossly: the lungs are grey, heavy, and solid; dry and granulomatous on the cross-section
		- microscopically: numerous neutrophils, macrophages, desquamated epidermis, and single erythrocytes found in the alveolar lumen and fibrin mesh
* yellow hepatization**(*hepatisatio flava*)**
	+ - grossly: the lungs are yellow, non-aerated and solid
		- microscopically: fatty degeneration of the neutrophils, macrophages and desquamated epidermis, and degeneration of these cells with the release of enzymes
* resolution stage **(*stadium decrementi*)**
	+ lysis/liquefaction/resorption **(*stadium resolutionis s. lysis*)***:* rare in animals
	+ organization with the connective tissue/carnification**(*carnificatio pulmonum*)**
	+ demarcation with the connective tissue band, abscessing or necrosis.

**Fibrinous serositis:**

* *pericarditis/peritonitis/pleuritis*
* *perisplenitis/perihepatitis*
* *polyserositis*

**Stages of development:**

* fibrinous exudate with a dose of a serous component **(*inflammatio sero-fibrinosa*)**
* absorption of the liquid phase - fibrinous (dry) inflammation **(*infammatio fibrinosa sicca*)**. During the initial stage, the serous membranes are opaque, dry, and coarse; when more fibrin is being accumulated, the serosa starts resembling “bread with a thick butter layer”
* neutrophil infiltrations, dissolution, and resorption of fibrin/organization of fibrin with the granulation tissue
* development of adhesions **(*synechiae s. adhesiones*)**
* formation of synechiae (***accretiones*)**/milky spots **(*maculae lactae s. maculae tendineae*)***;* it the process is located on the surface of a given organ, there is:
	+ development of focal synechiae resembling a rope **(*accretiones funiculares*)***,*
	+ total accretion of the serosa **(*concretio cavi s. obliteratio*).**

**Purulent inflammation (*inflammatio purulenta*)**

This is a type of exudative inflammation with the accumulation of purulent exudate, namely pus **(*pus*)***.*

Pus:

* is a turbid fluid, with creamy, yellow, green, or blue colour
* is composed of:
	+ a cluster of pyogenic bacteria (*Streptococcus spp., Staphylococcus spp., Pasteurella spp., Fusobacterium spp., Actinomyces pyogenes, Actinobacillus equiruli, Enterococcus*) and their toxins
	+ neutrophilic granulocytes at different degradation stages and their proteolytic enzymes
	+ cells of the given tissue, necrotic, digested by the proteolytic enzymes, and damaged by bacteria
	+ liquid phase originates from the blood vessels and body fluids.
1. **Superficial purulent inflammation (*inflammatio purulenta superficialis*)**
* pyorrhoea **(*pyorrhoea*):** purulent inflammation of the serous membranes
* empyema **(*empyema*):** accumulation of pus in the body cavities.
1. **Deep purulent inflammation (*inflammatio purulenta profunda*)**
* purulent infiltration **(*infiltratio purulenta*)**
	+ focal
		- micro-abscess **(*microabscessus*)**
		- abscess **(*abscessus*)**
* diffuse
	+ - phlegmon **(*phlegmone*):** purulent inflammation of the loose connective tissue
		- pyaemia **(*pyaemia*):** with inflammation of the blood and lymphatic vessels.

**Abscess (*abscessus*)**

Focal deep purulent inflammation that involves the accumulation of pus in a cavity that has developed as a result of proteolytic degradation of the tissue by the enzymes released from the dead neutrophilic granulocytes, with bacteria or without their involvement - this is called a sterile abscess **(*abscessus sterilis*)**.

Stages of abscess development:

1. At the site where pyogenic bacteria are present, inflammatory exudate starts accumulating; this exudate is rich in the neutrophils – purulent infiltration **(*infiltratio purulenta*)**.
2. Bacteria are phagocytized, neutrophils die, and afterwards, proteases are released from the dead granulocytes; these enzymes digest the damaged cells and the cells surrounding the focus of inflammation, which initiates the accumulation of purulent exudate with resulting liquefaction of the tissue and formation of an immature abscess **(*abscessus immaturus*)**.
3. Following necrosis and liquefaction of this focus, mature abscess **(*abscessus maturus*)** develops, and pus accumulates. At the periphery, the endothelia are budding and fibroblasts are proliferating; the granulation tissue is growing, and with time, it becomes fibrotic, forming a connective tissue pouch, which serves as a barrier preventing further expansion of the infection. On the inside, a lining is developed called the pyogenic membrane **(*membrana pyogenes*)**since it is being infiltrated by the leukocytes with the enzymes that digest the lining and more pus is produced.

Regression of abscess:

* small abscesses can be entirely liquefied and absorbed
* larger abscesses: following the absorption of liquid components, the connective tissue pouch shrinks and a scar develops at the site of the former abscess
* abscesses may rupture, with fistula formation
* can undergo calcification

the connective tissue pouch becomes hypertrophic and thickens and transforms into a pseudocyst.

**Purulent pneumonia (*bronchopneumonia purulenta*)**

This pathology consists of the accumulation of pus in the lung tissue (initially as the neutrophilic infiltration), i.e. in the bronchi, bronchioles and inside the alveoli – this is an infiltrative type of the inflammation: diffuse **(*bronchopneumonia purulenta infiltrativa*)**or focal **(*bronchopneumonia purulenta abscedens*);** abscesses of different sizes develop and they are often surrounded by connective tissue and located in poorly aerated zones of the lungs. Both types of pathology often coexist.

The lungs are infected with pyogenic bacteria by airway transmission, and from the bronchi, the infection expands onto the pulmonary tissue with a capacity for abscess formation, or by hematogenous transmission from an extrapulmonary and metastatic site of the infection. The bronchial and alveolar epithelium is damaged by the bacterial toxins and enzymes released from dead neutrophils; the tissue architecture becomes blurred and obscure, and the necrotic foci are filled with pus while the periphery is demarcated with the connective tissue.

**Purulent infiltrative pneumonia** **(*bronchopneumonia purulenta infiltrativa*)**

* purulent exudate is found in the alveolar lumen, bronchioles and interstitium
* the respiratory epithelial cells of the alveolar walls and the blood vessels of the alveolar septa are damaged
* progressively, the lung tissue pattern becomes obscure.

**Purulent focal pneumonia (*bronchopneumonia* *purulenta focalis*)**

Grossly: the abscesses develop in the lungs, protruding from their surface in a semi-circular manner while the pleura is initially opaque and thickened in these sites.

Microscopically: initially, small foci of neutrophilic infiltration – micro-abscesses **(*microabscesses*)***,* with resulting abscess **(*abscesses*)** development.

**Purulent hepatitis (*hepatitis purulenta*)**

This type of inflammation usually presents as abscesses **(*hepatitis purulenta apostematosa s. abscedens*)**and results from the primary infection with pyogenic bacteria (direct exogenic or endogenic, e.g. by the foreign bodies in the reticulum, damage to the liver) or a metastatic secondary infection. The secondary abscessed may have a haematogenic, choleretic or lymphogenic origin and may spread from the surrounding sites. Bacteria sometimes get to the liver via parasitic larvae.

New abscesses are bright yellow, green-yellow, or grey, filled with creamy-like, scentless or fetid pus, and are brightly demarcated from the healthy tissue. Older abscesses are surrounded with a pouch of the connective tissue, of varied thickness, and their content may become thicker, harder, and calcified, which resembles mortar. Haematogenic abscesses are usually multiple.

**Purulent nephritis (*nephritis purulenta*)**

The kidneys are infected with pyogenic bacteria via:

* haematogenic transmission: the pathogens enter the kidneys from the lungs, umbilical cord, limbs, or heart as the aggregates or parts of the infected thrombi. The glomerular emboli develop, which results in purulent glomerulonephritis **(*glomerulonephritis purulenta*)**; the emboli may occur in the interstitium and the pathology is then called purulent interstitial nephritis **(*nephritis interstitialis purulenta*)**
* urogenous transmission: the inflammatory process spreads from the renal medulla into the interstitial tissue, which is called purulent pyelonephritis **(*pyelonephritis purulenta*).**

The pathology can be diffuse **(*nephritis purulenta diffusa*)**or focal **(*nephritis abscedens*)**.

Grossly: the kidney is enlarged, mottled with multiple purulent foci both on the surface and the cross-section (small spots, nodules), which are yellow and with small amount of pus on the cut surface. Small foci are prone to coalescing, with the formation of large abscesses.

Microscopically: infiltration with neutrophilic granulocytes in the glomeruli and/or the intratubular connective tissue. Purulent exudate can be also found in the renal convoluted tubules (as casts), especially the distal and collecting tubules. Large amounts of neutrophils accumulate near the bacterial clusters and penetrate them, with resulting cell degradation (in the convoluted tubules, glomeruli, connective tissue, and blood vessels) and blurred renal pattern at the disease sites. The connective tissue surrounding the purulent foci proliferates, and the blood vessels become dilated.