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Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
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Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Воспаление**

Theme: **Inflammation**

Время 3 ак. часа

Actuality of the theme. Knowledge of clinical features of inflammation is necessary for differential diagnostic of inflammatory illnesses. It is necessary to remember that appearance of all five classical features is typical only for acute inflammation of the skin and mucous membranes. If inflammation arises in the inner organs these features are expressed weakly. In those cases it is necessary to take into consideration general signs of inflammation. Some features can be absent in chronic inflammation and it makes the right interpretation of the inflammation character much difficult.

Learning goals of the lesson: consider the stereotypical response mechanisms of tissue reaction and try to identify the features of implementation of this reaction at subcellular and cellular levels.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know mechanisms for formation of a response to a damaging agent.
2. To know components of Celsus-Galen's pentad and principles of forming each of components.
3. To know and understand peculiarities of microcirculatory reaction in focus of inflammation.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. microcirculation structure; cell structure, role of lysosomes, phagosomes in cell functioning (histology, cytology, embryology disciplines).

Control questions of the lesson:

1. Inflammation: definition, etiology, types, signs and main components.
2. Primary and secondary alteration in inflammation. Mediators of inflammation.
3. Changes in blood flow in the focus of inflammation: stages and mechanisms of development.
4. Mechanisms and importance of exudation in the focus of inflammation. Types of exudates.
5. Marginal standing and emigration of leukocytes in the inflammatory focus, their mechanisms.
6. Phagocytosis: types, stages, mechanisms and biological significance. Violation of phagocytosis: causes and significance in inflammation.
7. Proliferation, its main manifestations and mechanisms of development.
8. Chronic inflammation, patterns of development.
9. Outcomes of inflammation. Principles of anti-inflammatory therapy.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Inflammation is the most often met typical pathological process.

Inflammation — is a typical pathological process, which is characterized by a complex of morphological, biochemical and functional changes and the reaction of microcirculation and connective tissue in response to the tissue damage.

Theories of inflammation.

1. Theory of Virkhov: explains inflammation thus: part of cells destroyed by inflammation, as result the products of disintegration are formed, which stimulate reproduction of the second cells. Where is alteration, then is proliferation.

2. Vascular theory of Kongeym: in the area of inflammation there are vascular reactions (violation of microcirculation) due to which leucocytes from blood emigrate in the area of inflammation.

3. Parasite theory of Mechnikov: without leucocytes there is not inflammation, a leucocyte is an inalienable attribute of inflammation. At acute inflammation neutrophiles emigrate in the area of inflammation, at chronic are monocytes.

4. Physical and chemical theory of Shade: in the area of inflammation there are difficult physical and chemical changes as acidosis, disionia (high blood pressures), which lie in basis of inflammation. At acute inflammation of pH low, can = 6,5; at chronic – 7,0-7,2 (in N – 7,34). If there is inflammation there is acidosis.

5. Biochemical theory of Menkhen: in an area inflammations appear biologically active matters by a biochemical way. These matters are adopted mediators of inflammation. Without mediators of inflammation – there is not inflammation.

The inflammation reaction development depends on:

1. the location of the phlogogen agent action
2. the inflammation beginnings location
3. the organism reactivity defines
4. the inflammation beginnings
5. the inflammation clinical course
6. the inflammation outcomes

Etiology

Factors, which cause inflammation divided on: 1) exogenous and 2) endogenous.

1) Exogenous factors:

- a) factors of physical origin (mechanical, thermal, ionizing and ultraviolet radiations);
- b) chemical factors (acids, alkalis, salts of heavy metals, phenols, aldehydes, etc.);
- c) biological agents (viruses, bacteria, fungi, protozoa).

2) Endogenous factors:

- a) products of the broken metabolism (nitrous connections - at uremia, urinary acid - at a gout));
- b) hemorrhages and products of disintegration (destruction) of blood cells;
- c) immune complexes (a complex is an antigen-antibody, components of complement and others).

Classification of inflammation:

1) By clinical course:

- a) acute
- b) subacute,
- c) chronic.

2) By reason:

- a) uninfected origin (banal or unspecific) – caused uninfected factors;
- b) infectious origin (tuberculosis, syphilis, lepra, scleroma, glanders).

3) By character of predominating phase of inflammation:

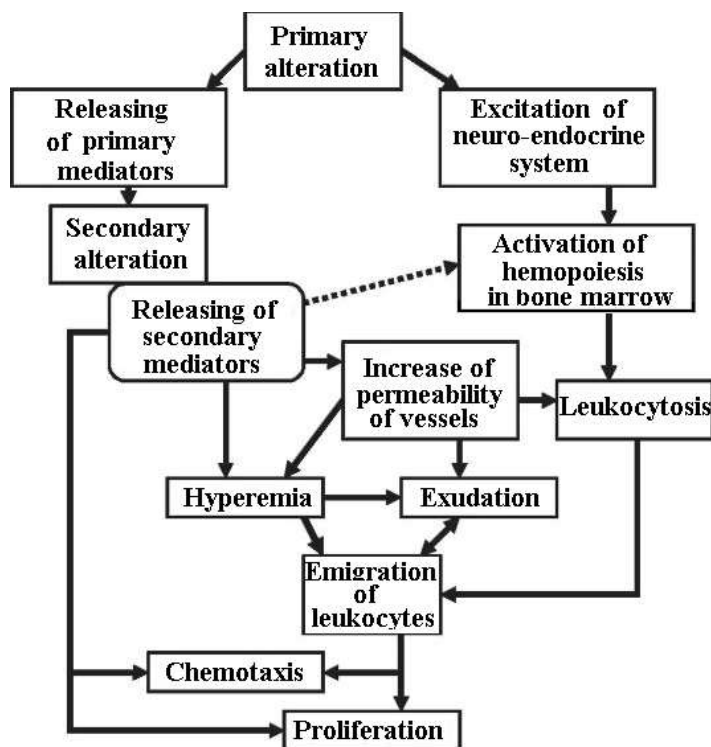
- a) alterative
- b) exudative,
- c) proliferative inflammation.

4) In dependence on reactivity of organism of inflammation can be:

- a) normoergic - adequate after the displays of factor which caused it;
- b) hyperergic - is stormy(violent) course of inflammation, for example, on a background (against a background) sensitizing;
- c) hypoergic – with insignificant displays (for the children of 1th month of life, in senile age, at considerable exhaustion of organism).

Components of inflammation (Stages)

Alteration, exudation and proliferation are referred to the components of inflammation



Alteration

Alteration is an injury of cells structure and functions impairment, an organs impairment, a systems impairment, a metabolism impairment leading to the vital activity impairment.

Primary alteration

It arises in case of the phlogogen factor action and it is characterized by the metabolism impairment, morphological and functional impairments, usually it locates in the inflammation epicenter.

Secondary alteration

It arises as a consequence of the surrounding tissues and the whole organism response (it may arise in case of the phlogogen factor action if the phlogogen factor action continues. Mostly it marked in the peripheral part of inflammation (around the primary alteration zone)).

Table 1. Differences of primary from secondary alteration

Zone of primary alteration	Zone of secondary alteration
Cause	
Phlogogenic agent	Phlogogenic agent; physical chemical factors, metabolic changes in zone of primary alteration; action of inflammation chemical mediators
Localization	
Localization of direct phlogogenic agent action	Periphery of direct phlogogenic agent action, region around the zone of primary alteration
Mechanisms of formation	
Injury and destruction of tissue structure, metabolism impairments (catabolism prevalence), substantial physical chemical changes	Impairments of nervous system control, axon transport, trophic and plastic factors, vascular tone and blood flow, and action of inflammation chemical mediators
Time of forming	
Strait out after the direct action of phlogogenic action	In some seconds-minutes after the direct action of phlogogenic agent
Manifestations	
Mostly irreversible	Reversible

Mediators of Inflammation

By origin:

- cell
- plasma

I. Cell mediators of inflammation			
1. Previous cell mediators of inflammation			
groups of mediators	mediators	sources of mediators	effects
vasoactive amines	histamine	basophils mast cells	vasodilation; an increase in vascular permeability; spasm of smooth muscles
	serotonin	thrombocytes	Itches; granulocyte inhibition; stimulation of monocytes-macrophages and fibroblasts
lysosomal factors	proteinases	granulocytes monocytes-macrophages	tissue destruction; stimulation of emigration and phagocytosis; stimulation of monocytes-macrophages and fibroblasts; proliferation and activation of lymphocytes
	non-enzyme cationic proteins	granulocytes	Microbicidity; an increase in vascular permeability; mast cell degranulation; adhesion and migration of leukocytes
neuropeptides	substance P calcitoninogen related peptide neurokinin A	C-fibers of afferent neurons	Vasodilation; an increase in vascular permeability; mast cell degranulation; spasm of smooth muscles
neuromediators	acetylcholine	cholinergic mediators	Vasodilation; smooth muscle spasm; stimulation of leukocytes
2. newly synthesized cell mediators of inflammation			
arachidonic acid metabolites	prostaglandins	monocytes-macrophages granulocytes thrombocytes	activation of leukocytes; vasodilation; pain
	thromboxanes	monocytes-macrophages granulocytes thrombocytes	aggregation of thrombocytes; spasm of smooth muscles; activation of granulocytes leukocytes; an increase in vascular permeability (LTC ₄ , D ₄ , E ₄); vasodilation
	leukotrienes lipoxins	monocytes-macrophages granulocytes thrombocytes	activation of smooth muscle spasm(LTC ₄ , D ₄ , E ₄ , lipoxins)
phospholipids	PAF (platelet activating factor)	granulocytes mast cells monocytes-macrophages	smooth muscle spasm; vasodilation; an increase in vascular permeability; activation of leukocytes; aggregation of thrombocytes
monokines	interleukin-1 TNF	monocytes-macrophages	activation of leukocytes and other cells; proliferation and activation of lymphocytes; stimulation of phagocytosis; stimulation of proliferation and activation of fibroblasts; stimulation of tissue destruction
lymphokines	macrophage activating factor macrophage inhibiting factor. Il-2	T-lymphocytes	activation and inhibition of granulocytes; stimulation of lymphocytes and granulocytes; activation of NK-cells
oxygen active forms	superoxide anion,	granulocytes monocytes-	tissue destruction; granulocyte activation; phagocytosis stimulation; Inhibition of monocytes

	perhydroxyl-anion, hydroxyl-anion, singlet oxygen, hydrogen dioxide, hypochloride	macrophages	
the other small molecules	nitric oxide	monocytes- macrophages granulocytes	tissue destruction ; granulocyte activation
II. Plasma mediators			
kinins	bradykinin	plasma interstitial fluid	increase in vascular permeability ; smooth muscle spasm; inhibition of granulocytes; stimulation of lymphocytes and fibroblasts; pain
factors of blood coagulation	fibrinopeptides products of fibrin degradation	plasma	activation of leukocytes; phagocytosis inhibition
Complement components	C5b–C9 C5a des Arg C5a–C3a	plasma interstitial fluid	tissue destruction (C5a–C9); leukocyte activation; increase in vascular permeability (C5a, C3a); smooth muscle spasm

Acute phase response is a system organism protection

Acute phase response is a number of the numerous systemic reactions developing in response to injury, this reactions are caused by the main protective and control organism systems involving (nervous system, endocrine system, immune system).

This reactions are accompanied by the physiological functions co-ordinate reorganizations, the metabolic resources repartition for the injury protecting of organism.

The acute phase response development scheme

1. Tissues injury
2. Inflammation
3. Activation of leukocytes, fibroblasts, endothelial cells
4. The mediators secretion
5. The mediators action on the target cells
6. The systemic reactions
 - NS — hypothalamus — fever
 - Endocrine system — pituitary gland — adrenocorticotropin
 - Liver — the acute phase proteins
 - Hemopoietic system — bone marrow — leukocytosis, reticulocytosis
 - Immune system — leukocytes activation

Acute-phase proteins classification (APP)

Assortment of APPs based especially on functional criteria:

Plasma proteins with increased concentration during the acute phase response (**positive acute-phase proteins**):

- Protease inhibitors: α 1-antitrypsin, α 1-antichemotrypsin;
- Coagulation proteins: fibrinogen, prothrombin, factor VIII, plasminogen;
- Complement proteins: C1s, C2, B, C3, C4, C5, C6, C9, C1, and INH;
- Transport proteins: haptoglobin, hemopexin;
- Other proteins: CRP, SAA, α 1-acid glycoprotein, Gc-globulin, ceruloplasmin.

Plasma proteins with decreased concentration during the acute phase response (**negative acute-phase proteins**):

- Protease inhibitors: inter α 1-antitrypsin;
- Complement proteins: properdin;
- Lipoproteins: lipoproteins with high density, lipoproteins with low density;
- Other proteins: albumin, prealbumin, transferrin

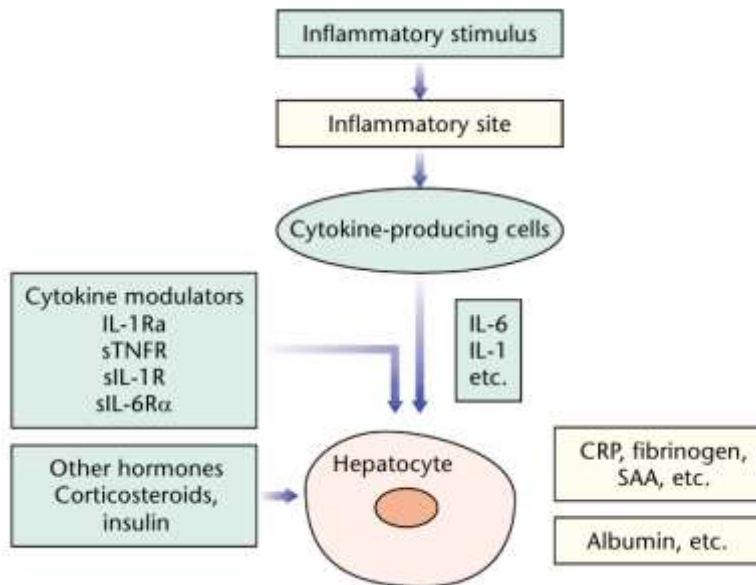


Figure 1 The acute-phase protein response is regulated both directly and indirectly by a complex network of intercellular signalling molecules involving cytokines, cytokine modulators and other hormones. Inflammation-associated cytokines, produced by cells at the inflammatory site and probably by distant cells as well, induce changes in production of acute-phase proteins by hepatocytes.

The protein fractions change:

- hypoalbuminemia
- hyperglobulinemia
- an increase in α - and β -globulins
- an increase γ -globulins

The main acute-phase proteins (APP)

C-reactive protein (CRP) is the most important APP. CRP is a α -globulin characteristic to vertebrates. CRP is the first protein described in relation with an acute pathological process with resultant of the entire group name. Binding of CRP to the bacteria, fungi and parasites membranes are dependent to Ca^{2+} , being associated with the classical activation pathway of the complement, resulting C3b formation. After interaction with various ligands, CRP exerts other functions, similar to antibodies - like agglutination - but without specificity. CRP reacts also like opsonin. It amplified chemotaxis mechanisms and macrophages and neutrophils phagocytosis. CRP binds damaged cells nuclear chromatin, participating in degradation of their nuclear components. CRP also binds some endogenous compounds, like membrane phospholipids. Similar to other APPs, CRP is synthesized by hepatocytes, synthesis amplified in acute infections, inflammations, neoplastic and autoimmune diseases, and diseases with immune complexes. In these pathological conditions, CRP serum concentration increases rapidly, being obvious in a few hours after infection. Conclusively, CRP has nonspecific functions, independent to immune system, in early response and defense mechanisms against infectious diseases and other pathological conditions.

Coglutinin (CGT) is an ample plasma molecule which binds C3b of the complement in multiple combination sites; thereafter, CGT contributes in agglomeration (coagglutination) of C3B covered particles, followed by their phagocytosis and elimination.

Serum amyloid A (SAA) has various functions, including decrease of IL-1 and $\text{TNF-}\alpha$, inhibition of thrombocytes aggregation, and inhibition of oxidative reaction in neutrophils. Higher plasma concentration of SAA determined amyloidosis, disease characterized by deposition of this APP in various tissues, in fibrils that interfere with normal functions of the organs (e.g. myocardial contraction and glomerular filtration).

α 1-acid glycoprotein (α 1-AGP) suppresses lymphocytes blastogenesis response and antibodies synthesis.

β 2-macroglobulin (β 2-M) is a proteases inhibitor, neutralizing neutrophils and macrophages lysosomal hydrolases, similar to other anti-proteases.

Ceruloplasmin (CPL) eliminates neutrophils superoxides

Fibrinogen (FNG) is implicated in coagulation and wounds healing. Higher concentration of FNG determined erythrocytes agglomeration, fast deposition, and increase of their sedimentation velocity.

Haptoglobin (HGB) inhibits bacterial development by binding iron, depriving bacteria of this element. In some species, authors describe other acute-phase proteins.

II. Exudation

Second stage include:

1. vascular reactions
2. exudation
3. migration of leukocytes
4. phagocytosis

Vascular Reactions

Change of microcirculation in inflammatory center:

- The short – term spasm
- Arterial hyperemia
- Venous hyperemia
- Stasis

Short-Term Spasm

The short-term spasm of arterial vessels is an angiospastic reaction of reflex nature. It is an unspecific initial reaction of vessels to any damage and has protective value due to limitation of pathologic substances entering into organism from the damaged locus. Sometimes in clinical practice a physician applies a cold at the very beginning of inflammation in order to stop the process. Sometimes it is actually useful. But usually this stage is short-term and substituted by more significant changes in microcirculation.

Arterial hyperemia

Arterial hyperemia supplies the locus of inflammation with additional volume of oxygen, substrates and additional quantity of leukocytes.

Venous hyperemia

Venous hyperemia inevitably follows the arterial one. The blood stream slows down, and leukocytes occupy boundary position near the wall. It means, that chemotaxic substances, which are formed in the center of inflammation, influence the leukocytes located in the bloodstream. The adhesive proteins, which are formed in endothelium, make the surface of endotelocytes and leukocytes more “sticky”

Stasis

Stasis (stopping of blood flow in the capillaries) provides the leaving of leukocytes from vessels into the center of inflammation. The permeability of vascular walls to plasma proteins and leukocytes considerably rises. Without slowing of the blood flow, boundary position of leukocytes and increasing of permeability, the phenomenon of emigration of leukocytes and further phagocytosis are impossible.

Exudation

Mechanism of exudate formation:

- Increased vessel wall permeability
- Increase of filtrational pressure in venous part of capillaria and venuli
- Intensification of ultrapinocytosis
- Increase of osmotic and oncotic pressure in inflammatory focus

Reasons of increase of permeability of vascular wall are in the area of inflammation:

- a) products of degranulation of tissue's basophiles (histamine and serotonin)
- b) kinins (bradykinin and kallidin), c) prostaglandins and some leukotriens,
- d) lisosomal enzymes (elastase, collagenase, hialuronidase) and unenzymic cationic proteins,
- e) fibrinopeptid and products of degradation of fibrin, f) acidosis.

There are some mechanisms of increase of permeability of vascular wall at inflammation:

- a) activating of microvesicular transport through endothelium cells
- b) formation of transcellular channels in endothelium,
- c) multiplying the slits between endothelium (takes place as a result of reduction and rounding off of endothelium),

d) desquamation (loosen) of endothelium which is the display of primary and secondary alteration and others.

Differences of serous exudate from transudate

Properties	Serous exudate	Transudate
Specific gravity	1,018 and >	< 1,012
Albumen in %	> 3%	< 3%
Mucus in %	> 0,2%	< 0,2%
Capability to coagulation	Coagulates, contains the blood coagulation factors	No
A common amount of cells is in 1 mm ³	300 and >	< 100
pH	< 7,0	7,4 – 7,6 and >
Osmotic pressure	0,6 – 1 and >	Less

Serous exudate appears at serous inflammation of mucous and serous membrane. Transudate may develop only without inflammation. And the main mechanism of them is increase of hydrostatic pressure in vessels.

Types of inflammatory exudates

1.Serous exudate - primarily a clear fluid, low in protein (mainly albumin) which exudes from serosal or mucosal surfaces because of mild irritation. Such an exudate can also be located within body organs. Neutrophils can be present in considerable number, in which case there will be whitish appearance to the exudate. The initial exudate in many inflammatory reactions is serous.

2.Fibrinous exudate - exudation of a fluid rich in fibrinogen which will clot to form a yellowish gel. Usually occurs with severe vascular injury and is seen more commonly on mucosal and serosal surfaces such as intestine, pleura, peritoneum, and synovial membranes. Fibrinous pneumonia is also an example. Because fibrin is chemotactic large number of neutrophils are usually present. Where two opposing surfaces have a fibrinous exudate between them, the organisation of the fibrin leads to adhesion. Viewed microscopically the fibrin may appear as solid clumps or long delicate strands. In severe mucosal damage where the epithelium is lost the fibrin that accumulates may become adhered to the remaining mucosa.

3.Haemorrhagic exudate - haemorrhage is prominent and therefore such an exudate occurs where the blood supply is abundant, and there is severe damage to the terminal vascular bed. The term must not be confused with haemorrhage alone, which can occur without any inflammatory reaction.

4.Catarrhal or mucopurulent exudate - occur on mucous membranes and mucosal surfaces of the alimentary, respiratory, and reproductive tracts. Characterised by the outpouring of large amounts of mucous that is accompanied by neutrophils, tissue debris, fibrin and sometimes red blood cells. Other signs of inflammation are present in the underlying mucosa.

5.Purulent or suppurative exudate - characterised by the production of pus (suppuration) which may be defined as a thick creamy fluid composed of large numbers of viable and necrotic polymorphs, which is partially liquefied by hydrolytic enzymes released from dead leucocytes. It is a characteristic response to certain types of bacteria that are "pyogenic" (pus forming).

6. Ichorous exudate contain anaerobic microorganisms

7. Combined forms of exudate-serosis-fibrinous, purulent-fibrinous, purulent-haemorrhagic

Cells in the inflammatory exudate:

Neutrophils - first cells to migrate in large number to the tissue and are aggressively phagocytic. Attracted to the site of injury by chemotactic factors. Where a bacterial infection is the cause of inflammation, neutrophils migrate to the tissues in very large number. They will endeavor to limit the spread of infection. Neutrophils have a very short life span irrespectively of cytotoxic factors (24-48 hours in tissues following a half-life blood circulation time of about six hours). Large numbers of dead and dying neutrophils are the chief constituents of pus. The fluid nature of pus is due to the liquefactive effect of lysosomal enzymes. Neutrophils phagocytose particulate matters and they can degranulate releasing enzyme-laden granules into the tissues at local sites of inflammation with the formation of chemotactic factors. In dying all their lysosomal enzymes are released, and this helps liquefy cellular

debris and fibrin as a prelude to repair. Enzymes released include alkaline phosphatase, lysozyme, myeloperoxidase, beta-glucuronidase, alpha-mannosidase and proteinase.

Eosinophils - react to stimuli similar to those for neutrophils. Granules contain with a few exceptions an assortment of enzymes similar to neutrophils. They are phagocytic like neutrophils but are more prominent in certain inflammatory reactions such as in parasitic infections and in allergic reactions. Antigen-antibody complexes attract eosinophils when arrested in the tissues. The antigens of parasites because of their bulk persist longer and attract eosinophils. Apart from parasitic disease, the presence of eosinophils in an inflammatory reaction in great number is not consistent. They are found in some granulomas (e.g., eosinophilic granulomas in cats), in eosinophilic myositis, and in the meninges of pigs with salt poisoning. They also have some neutralising effect against histamine, but it is probably not a major role.

Basophils - similar in form and function to the tissue mast cells. Circulatory numbers in the blood are very low. Basophils play a role in hypersensitivity reactions.

Lymphocytes - they are not phagocytic, and do not ordinarily migrate during the acute phase of inflammation, but may be many in the more chronic phase particularly where there is mucous membrane involvement. Lymphocytes are associated with the host's immune response and are often present in lesions around small blood vessels where they form a cuff.

Plasma cells - tend to be found in areas of more chronic inflammation and are usually present along with lymphocytes, macrophages and fibroblast. The formation of mature plasma cells from lymphocytes (B-cells) requires 4-5 days. The nucleus is displaced to one side and the cytoplasm has a clear halo on one side of the nucleus. It produces antibodies and their presence in an inflammatory reaction usually reflects a subacute or chronic process. Plasma cells are also found in high number in lymph tissue that is producing antibody to any antigen.

Monocytes (macrophages) - less common in blood than neutrophils. Although they arrive at the site of inflammation later than the polymorphs (granulocytes), they start to emigrate simultaneously. Their movement is slower but they are responsive to chemotactic influences. They are much longer-lived than the polymorphs. Their numbers are augmented by local mitotic proliferation of histiocytes (a histiocyte is a macrophage present in tissues which is derived from blood monocytes made in the bone marrow). The macrophages are more efficient than the polymorph at phagocytizing fibrin and cellular debris from the site of inflammation in preparation for repair. They process many antigens before transferring them to lymphocytes for antibody production. If antigens are readily broken down the macrophages do not persist. If difficulty in this process is encountered then the macrophages will persist in the lesion. They respond to a variety of stimuli, such as antigen-antibody complexes, complement, and bacterial and neutrophil products also immune and non-immune stimuli. Macrophages may divide in tissue to form other macrophages or may form epithelioid or giant cells.

Epithelioid cells - formed from macrophages with similar appearance, but lie closer together and take the shape and arrangements similar to prickle cells in the epidermis. The cytoplasm is eosinophilic and the cell membrane is indistinct. They do not appear to phagocytize but probably work at destruction of the irritant by secretion. It is common in many granulomatous types of inflammatory reactions (see later).

Giant cells - formed by the cytoplasmic fusion of macrophages found in reactions to certain organism such as the tubercle bacillus. Thought to be poorly phagocytic and probably have a life span of only a few days.

Fibroblast - fibroblasts are found during the repair phase and will produce new fibrous tissue. They arise from undifferentiated mesenchymal cells mostly about blood vessels. Fibroblast multiplies rapidly in situ and secretes globular proteins that precipitate as macromolecular collagen fibres in the interstitium. Tissue lost through necrosis can only be replaced by proliferation of remaining viable epithelial cells or by fibrous repair. Fibrous proliferation will also occur in many chronic inflammatory processes particularly where there are large defects in tissue, due to the persistence of an irritant.

Migration of leukocytes

Stages of emigration of leukocytes:

1. margination
2. rolling

3. adhesion in vessels wall (molecules of adhesion: selectins, adherins, integrins, Ig super-family)
4. diapedesis
5. migration in interstitial tissues towards a chemotactic stimulus
6. chemotaxis
7. leukocyte activation

Mechanisms of emigration. Following advance, leukocytes move along endothelial surface, insert pseudopods into junctions and assume a position between endothelial cell and basement membrane; eventually they transverse basement membrane and escape into extravascular space.

Molecules of the cells adhesion

name	functions
selectins	begins the interaction between leukocytes and vessel's endothelium
adherins	join L-selectin in the leukocyte and endothelium interaction initiation
integrins	join molecules of adhesion on the cell and molecules of the extra-cellular marrix and providing the strong joining
immunoglobulin super-family	ligands for integrins

The stages of Le adhesion to endothelium

1. Leukocytic CD15 and E-selectin joining lead to the slowing down and stoppage of neutrophils, when neutrophils rolls on endothelium.
2. Fixed Le is activated because of the interaction with molecules and chemokines of endothelium.
3. Activation of Le leads to the integrins expression on it's surface for joining with ICAM – 1, which induces in case of endothelium activation.

Chemotaxis of Leukocytes.

After exiting the circulation, leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis, which is defined as locomotion oriented along a chemical gradient. Both exogenous and endogenous substances can act as **chemoattractants**.

Chemoattractants:

1. For neutrophils: C5a, Leukotriene B4, Bacterial products
2. For monocyte-macrophages: C5a and C3a, Leukotriene B4, Bacterial products
- Fractions from neutrophils: Lyphkines (generated by lymphocytes), Fibronectin products
3. For eosinophils: Eosinophilic chemotactic factor of anaphylaxis (ECF-A), Prostaglandin D2, Histamine

Mechanism of chemotaxis

Chemotactic factor binds to specific receptors on cell membrane of leukocytes → Activates phospholipase C (Mediated by a G protein) → Phospholipase C splits phosphatidyl inositol 4,5-biphosphate (PIP2) into inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG) → IP3 causes release of calcium, first from intracellular stores and then from influx of extracellular calcium → Increased cytosolic calcium triggers assembly of contractile elements responsible for leukocyte movement towards source of chemotactic factor (chemotaxis).

Cell that emigrate.

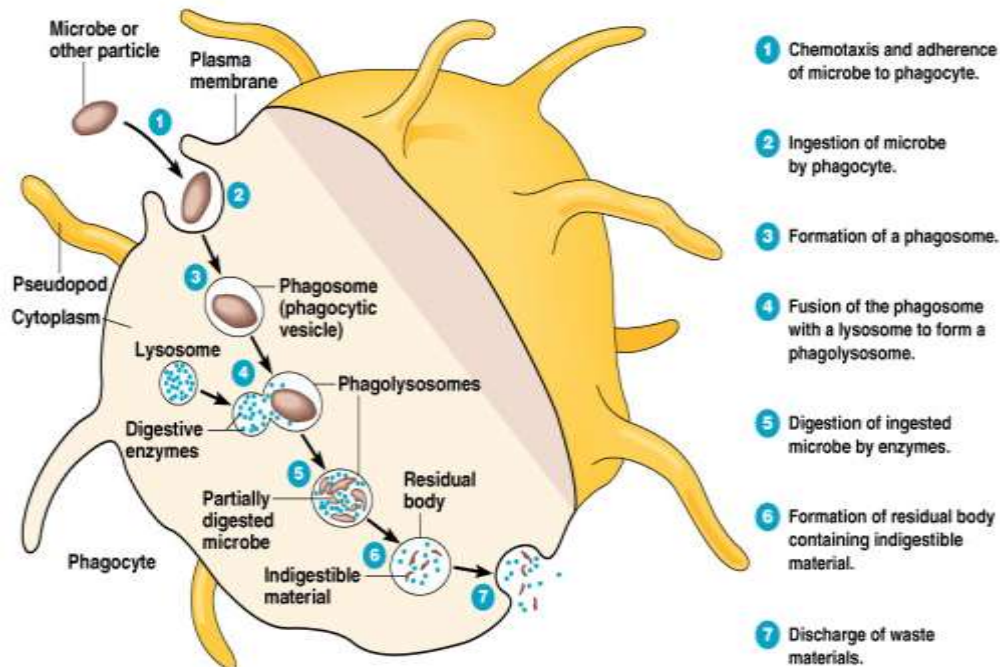
1. In bacterial infections, neutrophils first emigrate and persist for first 24 to 48 hours, then replaced by monocytes.
 2. In tubercule or typhoid bacilli infections, monocytes emigrate right from the beginning.
 3. In viral infection and immune reactions lymphocytes emigrate right from the beginning.
 4. In hypersensitivity reactions, eosinophils predominate.
- By 48 hours, monocytes replace neutrophils owing out three factors:
1. Neutrophils are short-lived and disappear after 24-48 hours; whereas monocytes survive for weeks to months.
 2. Monocytes emigration is sustained long after neutrophil emigration ceases.

3. Chemotactic factors for neutrophils and monocytes are activated at different phases of the response.

Phagocytosis

Currently there are two main classes of phagocytic cells:

- Macrophages: neutrophils, basophils and eosinophils;
- Macrophages: blood monocytes and derived from these tissue macrophages.



(a) Phases of phagocytosis

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The efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins, notably mannan-binding lectin, all of which are recognized by specific receptors on leukocytes.

Cleavage of exogenous substances, antigens, bacteria phagocytes depends phagolysosome lysosomal enzymes and of oxidative processes from changes in the cell. Catabolism of corpuscular substances is carried out lysosomal enzyme systems. Oxygen independent bactericidal action (carried out under anaerobic conditions, in phagocyte cytoplasm) have enzymes of leukocyte granules: lysozyme, lipases, nucleases, proteases, esterases, phosphorylase, and others. Catabolic process takes place inside the vacuole, so proprietary materials are not digested.

Oxygen independent bactericidal action of phagocytes carry also cationic protein and lactoferrin. Cationic proteins bind to proteins of bacteria and cause their death. Lactoferrin binds iron required for the metabolic processes of bacteria and it is causes a bactericidal effect.

Currently leading microbicidal factor of macrophages considered active form of nitrogen (NO-). Nitric oxide kill many types of microorganisms (viruses, bacteria, fungi, protozoa), and even tumor cells. Most intracellular infections (Chlamidia, Mycobacterium, Tixoplasma, Trypanosoma, Listeria) are very sensitive to NO.

Oxygen-dependent bactericidal action. Strengthening the metabolism of macrophages increases the oxidation of glucose, which is accompanied by the formation of large amounts of a bactericidal H₂O₂ highly reactive hydroxyl radicals (OH) and superoxide anion (O₂) that have expressed bactericidal activity against many kinds of microbes. To enzymes involved in oxygen-dependent bactericidal mechanisms include myeloperoxidase, catalase, and NAD NADF-oxidase and others.

Digested by phagocytes bacteria usually die and disintegrate - complete phagocytosis, but some microorganisms provided with a capsule or dense hydrophobic cell walls trapped by phagocytes, can be resistant to the action of lysosomal enzymes, or are able to block fusion of phagosomes and lysosomes.

For this reason they remain a long time in phagocytes in a viable state. This kind of phagocytosis called incomplete.

The underlying **causes and mechanisms of incomplete phagocytosis:**

1 Reducing the number of phagocytes:

a) hereditary forms:

- decreased granulocytopoiesis → neutropenia;
- hypoplasia of the spleen → monocytopenia.

b) congenital (autoimmune) neutropenia.

c) acquired neutropenia (for diseases with splenomegaly).

2 Ineffective granulocytopoiesis (qualitative changes of neutrophils)

a) violation of the phagocytes mobility (violations of the reversible polymerization of contractile protein of phagocytes - actin). Example: the syndrome of "lazy leukocyte"

- hereditary form;
- acquired form (with ↑ serum IgE, ↓ energy or ↓ cAMP in the cells).

b) disorders of phagolysosomes formation (hereditary defect in the formation of lysosomal granules - their fusion → giant granules). Example: Chediak-Higashi syndrome

c) violation of inactivation and destruction in phagocytes:

- hereditary deficiency of oxygen-dependent bactericidal mechanism (↓ NADPH oxidase and / or myeloperoxidase in phagocytes). Example: chronic granulomatous
- hereditary deficiency of oxygen independent bactericidal mechanism (↓ lysozyme, lactoferrin, cationic proteins in phagocytes).

3 Violation of object recognition by phagocytes:

- hereditary deficit / defect phagocyte receptors
- Acquired deficiency of opsonins and chemoattractant (severe liver disease, intoxication, etc..)

4 Violations of neurohormonal regulation of phagocytosis:

- adrenaline (in small doses) → ↑ phagocytosis;
- acetylcholine → ↓ phagocytosis;
- glucocorticoids → ↓ phagocytosis.

III. Proliferation

This stage include:

- reproduction of cells, that actually - proliferation;
- synthesis of noncellular components of connecting tissue: collagen, elastin, glycoproteins, etc.

These processes are accompanied the considerable strengthening of anabolic processes.

Regenerative capacity of tissues

The cells of the body have been divided into three groups based on their regenerative capacity:

Labile cells - continue to multiply throughout life to replace those shed or destroyed by normal physiological processes (apoptosis and necrobiosis). These include the cells of the epithelial surfaces, the lymphoid and haematopoietic cells. Included among the epithelial surfaces are the epidermis, lining of buccal cavity, gastrointestinal tract, respiratory tract, genital tract, and lining of ducts. In all these sites, the surface cells exfoliate throughout life and are being replaced every few days.

Stable cells - retain the latent capacity to regenerate, but under normal circumstances do not actively replicate because they have a survival time measured in terms of years and possibly equal to the life span of the individual. It includes the parenchymal cells of all glands in the body including the liver, the pancreas, salivary gland, endocrine glands, kidney tubular epithelia, glands of the skin, the mesenchymal cells of the body and their derivatives (e.g. fibroblast, chondroblast, osteoblast, and adipose tissue), endothelial cells, and smooth muscle cells.

Permanent cells - cannot regenerate and damage to these tissues represents permanent loss. It includes neurons, skeletal and cardiac muscle cells. However, in neuronal damage, the nerve cells are capable of replacing severed axonal processes but they must follow the pre-existing pathway of

degenerated axon. If not the re-growth may give rise to a mass of tangled fibres sometimes termed "amputation or traumatic neuroma" and is nonfunctional. Skeletal muscle and cardiac muscles are always replaced by scar tissue.

On the whole activating of proliferative processes is provided:

1) By the promoted synthesis BAS, which own the antiinflammatory influencing, in particular: a) inhibitors of hydrolase; b) antioxidants; c) poliamines; d) heparine, which represses adhesion and aggregation of blood cells, activity of kinines, biogenic amines, factors of complement; e) glucocorticoids.

2) Decrease in concentration in tissue of chalones – matters of albuminous origin which appear in mature cells and inhibit cellular division. At a damage and death of cells in the area of inflammation the concentration of chalones diminishes in tissue, accordingly liquidated their inhibited influence on the little differentiated cells (syn: stem cell). They begin to be divided and their division proceeds to the time, while the concentration of chalones will not be multiplied to the level, to characteristic for normal terms.

3) Increase in concentration of stimulators of proliferation (growth factors) in tissue. The factors of growth enter tissue from plasma of blood or are the products of cells which are in the area of inflammation.

Local signs of inflammation:

- **Redness** (arterial hyperemia + ↑oxyhemoglobin + ↑speed of blood flow → arterialization of venous blood)
- **Swelling** (↑↑ exudation and edema)
- **Heat** (↑intensity of redox processes)
- **Pain** (irritation of nociceptors by mediators, compression by hydropic fluid, ionic imbalance (extracellular ↑ H⁺ and K⁺), injury nervous endings and fibers by enzymes)
- **Loss of function** (changes in metabolism and regulation of organ and tissue, structural impairments)

Systemic signs of inflammation:

- **Fever.** Develops in investigation of selection neutrophiles and macrophages of so-called leukocyte's pyrogens (IL-1).
- **Leukocytosis** (↑ PNL in acute inflammation; Monocytes, Lymphocytes in chronic inflammation. Characterized the absolute increase of amount of neutrophiles in peripheral blood and change of leukogram to the left. In basis of this reaction the exit of leucocytes lies from the reserve pool of red marrow in blood (an action IL-1 and factor of necrosis of tumours), and also stimulation of lekopoiesis under act of colony-stimulating factor.)
- **Increase of erythrocyte sedimentation rate (ESR).** It is related to multiplying the amount of high molecular weight proteins (globulins, fibrinogen) in plasma of blood, that led to superficial negative charge of erythrocytes diminishes or change to positive and they aggregation increasing.
- **Intoxication** conditioned entering blood of products of alteration from inflammatory tissues.
- **Stimulation of immunological reactivity**
- **Stimulation of bone marrow**
- **Stimulation of hepatic function** (synthesis of acute phase proteins)
- **Disturbance of a self-sensation** (headache, insomnia, loss of appetite and capacity to work)

CHRONIC INFLAMMATION

Chronic inflammation occurs when there is persistent irritation or injury over a long period. It is often called proliferative inflammation because it is characterised by a proliferation of cells than exudation of cells and fluids. There is usually evidence of host attempt at repair, namely fibrosis.

Chronic inflammation may take several **forms**:

- 1] Chronic ulceration - where an ulcer is not repaired
- 2] Chronic abscessation - where there is fibrous encapsulation of pus
- 3] Chronic granulomatous inflammation - characterised by the formation of granulation tissue that is heavily infiltrated with macrophages, polymorphs, lymphocytes, and possibly plasma cells. Signs of exudation may be considerable in granulation tissue if the causative agent is still operative.

Types of granulomas:

1. Infectious, and noninfectious.
2. Foreign body granulomas and immune granulomas.

• Granulomatous inflammation is typical of reaction to poorly digestible agents elicited by tuberculosis, leprosy, fungal infections, schistosomiasis, foreign particles, etc.

Chronic inflammation arises under the following settings:

- **Chronic inflammation following acute inflammation** - when the tissue destruction is extensive, or the bacteria survive and persist in small numbers at the site of acute inflammation, e.g. in osteomyelitis, pneumonia terminating in lung abscess.
- **Recurrent attacks of acute inflammation** - when repeated bouts of acute inflammation culminate in chronicity of the process, e.g. in recurrent urinary tract infection leading to chronic pyelonephritis, repeated acute infection of gall bladder leading to chronic cholecystitis.
- **Chronic inflammation starting de novo** - when the infection with organisms of low pathogenicity is chronic from the beginning, e.g. infection with Mycobacterium tuberculosis.
- **Under certain conditions, immune reactions** are set up against the individual's own tissues leading to autoimmune diseases.

General features of chronic inflammation

1. **Mononuclear cell infiltration**, which include **macrophages, lymphocytes and plasma cells, eosinophils and mast cells.**
2. **Tissue destruction** or necrosis is brought about by activated macrophages by release of a variety of biologically active substances.
3. **Proliferative changes.** As a result of necrosis, proliferation of small blood vessels and fibroblasts is stimulated resulting in formation of inflammatory granulation tissue. There are four components of this process:
 - formation of new blood vessels (angiogenesis),
 - migration and proliferation of fibroblasts,
 - deposition of extracellular matrix,
 - maturation and organization of the fibrous tissue, also known as remodeling.

Types of chronic inflammation:

I. Nonspecific, when the irritant substance produces a non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis, e.g. chronic osteomyelitis, chronic ulcer.

II. Specific, when the injurious agent causes a characteristic histologic tissue response, e.g. tuberculosis, leprosy, syphilis, scleroma.

VALUE OF INFLAMMATION

Analysis of the clinical value of inflammation helps to estimate its dialectics. This process is simultaneously positive and negative. From one side, it is a fundamental protective response, self-defensive reaction, which contributes to damaged tissues restoration and survival of organism. From other side – patient suffers, his ability to work is disrupted, he is ill. It is potentially harmful. Part of cells, tissues, organs can be destroyed, and die. An overactive inflammatory response can cause death.

Systemic inflammatory response syndrome (SIRS)

Autoaggressive systemic inflammatory response → delocalized and dysregulated inflammation process → disorders of microcirculation → organ perfusion → secondary organ dysfunction

Diagnostic criteria of SIRS:

Symptoms	Assessed factors
Body t°	> 38°C or < 36°C
Pulse rate	> 90 /min
Rate of breathing / PaCO ₂ (arterial blood)	> 20 /min / PaCO ₂ < 32 mm Hg
WBC	> 12 ×10 ⁹ or < 4 ×10 ⁹

Questions for self-control of knowledge:

1. What is inflammation? What are main components of inflammatory process, types of inflammation.
2. What are mechanisms of local and systemic manifestations of inflammation?
3. Give a definition of "alteration". Explain changes in rheological properties of blood in inflammation, protein composition and physico-chemical properties of plasma proteins during inflammation.
4. Give a description of cellular and plasma mediators of inflammation. Explain relationship of various mediators in inflammatory process.
5. Name pro-and anti-inflammatory mediators.
6. Name stages of change in blood flow in inflammation, describe mechanisms of vascular reactions.
7. Describe changes in rheological properties of blood during inflammation, protein composition and physico-chemical properties of plasma proteins.
8. What are functions of leukocytes in inflammation? Describe mechanisms of leukocyte emigration.
9. Describe phagocytic process: types, stages mechanisms. Explain causes and mechanisms of failure of phagocytosis (Chediak-Higashi syndrome, chronic granulomatosis in children).
10. Name stimulators and inhibitors of cell proliferation.
11. What is relationship of local and systemic manifestations of inflammation?
12. What is role of inflammation for human body?

Tasks for self-managed student work:

1. Role of reactivity in inflammation. Inflammation and allergy.
2. Hereditary diseases of phagocyte system.
3. Immunological manifestations of systemic inflammatory response.
4. Phylogeny and ontogeny of inflammatory reaction.

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