**INFLAMMATION. FEVER.**

***Inflammation (Gr. phlogosis; Lat. inflammatio) is the complex reaction of organism (of vessels, connective tissue and nervous system) in response to injure caused by pathogenic factors (phlagogens).***

Inflammation as a typical pathological process has developed in the process of evolution and is characterized by three main, closely interconnected phenomena: tissue dystrophy (alteration), circulatory disorders (with exudation and emigration) and proliferation of cells. Since inflammatory reaction promotes elimination of the signs of injury and recovery of the integrity of tissues, inflammation may be regarded as one of forms of defense-adaptative reactions of the organism.

There is an ancient parable about the blind beggars that went to ‘see’ what is an elephant. One of them approached the elephant from the side, the second ran into its foot, the third-the trunk, the fourth-the tail and the fifth-the ear. When they came back and were asked what the elephant was like, the first beggar answered - like a wall, the second-a pillar, the third replied-a pipe, the fourth-a rope, and the fifth-a carpet. This parable may be applied to many pathological processes, and in the first place to inflammation. Inflammation is very intricate and many-sided phenomenon consisting of different processes. Each researcher pays more attention to one of these processes which he regards as the most important. That is why many different opinions and theories came to being concerning the significance, origin and mechanism of development of the inflammation.

Inflammation attracted attention of scientists beginning from the ancient times. Hippocrates (the v-iv centures B.C.) considered that inflammation was of decontaminating significance for the organism. In the purulent areas harmful agents perish. Inflammation was regarded as an independent disease connected with dyscrasia.

Hippocrates’ opinion about the essence of inflammation was prevailing view up to the XVIII century, and during this time only the description of the main signs of the inflammation were added: four signs of the inflammation (redness, swelling, heat, pain) were described by Celsus at the beginning of our era and the fifth one (dysfunction)-by Galenus in the II century A.D.

***In the etiology of inflammation different exogenous and endogenous phlogogenic factors play a part:***

1. Exogenous phlogogenic factors consist of mechanical (different types of mechanical traumas), physical (ionizing radiation, electric current, heat and cold), chemical (powerful acids and alkali, poisons), biological (pathogenous microbes, viruses, fungi, parasites, etc.) agents.
2. Endogenous phlogogenic factors include the end products of catabolism of nitric compounds (uremic gastritis, pericarditis), bile acids (damage to mucous and serious membranes in jaundice), products of disintegration of malignant tumours, immune complexes precipitant in tissues.

***In the mechanism of development (pathogenesis) of inflammation 3 stages are distinguished:***

1. ***Alteration (lesion) of cells and tissues.***
2. ***Exudation and emigration .***
3. ***Proliferation.***

This division is to a certain extent conventional, because many changes occur simultaneously or continue in several stages in the course of the inflammation. For instance, metabolic disorders occur at any stage of inflammation.

Alteration, vascular reactions (with exudation and emigration) and proliferation are distinctly marked by their clinical and morphological signs.

The successive stages of inflammation are interconnected and each preceding stage prepares the ground for the next one. For instance, damage to tissues results in liberation of mediators which, changing vascular permeability, promote exudation and emigration, etc.

Alteration is damage of tissues and cells in the focus of inflammation. Primary and secondary (late) alteration are distinguished. The primary alteration results from the direct influence of the pathogenic agent on the tissues and cells; it is the initial stage of the inflammation. The secondary alteration occurs during the subsequent development of the inflammation as a result metabolic and circulatory disturbances in the inflamed area.

Severity of the morphological changes caused by alteration depends on the type of tissue, properties and power of the pathogenic agent and reactivity of the organism. Inflammation may result in ultrastructural changes as well as necrobiosis and necrosis. The volume of mitochondria is increased (sometimes decreased), cristae are decomposed; form and size of endoplasmic reticulum are changed; the membranes of the cell nuclei are damaged, distribution of chromatin is disproportionate. Lysosomas are damaged, the hydrolytic enzymes become free and destroy the structure of cells.

Necrotic phenomena are most frequently resulted from considerable trauma, burn, action of strong acids and alkalis or influences causing changes in organism’s reactivity.

Frequently dystrophic tissue changes are almost unnoticeable, whereas other, for instance, vascular, inflammatory phenomena, are clearly marked. However, there are inflammations (especially parenchymatous inflammations), which are characterized mainly by dystrophic processes that predominante over all other phenomena.

Alteration of tissues is the main motive factor of the inflammatory process. But this stage does not continue long and soon is replaced by the following ones.

The metabolic disorders play an important part in the origination of the functional and dystrophic changes in the focus of inflammation.

In the center of the inflammatory focus where the injury to the tissue is most clearly pronounced, the oxidative processes are usually diminished, while in the other parts of the inflamed area increase in the oxidative processes and in metabolism are observed.

In the inflamed tissues carbohydrates are vigorously oxidized, at the same time anaerobic glycolysis is intensified. Subsequently the glycolysis increases still more owing to accumulation of leukocytes in the focus of inflammation which cause splitting of carbohydrates mainly anaerobically. .

The amount of oxygen absorbed by inflamed tissue exceeds that of carbon dioxide excreted by it, that is, carbohydrates are not always completely oxidized, and large amounts of underoxidized metabolites (lactic acid, etc.) accumulate in tissues.

Disturbances in fat and protein metabolism in the focus of inflammation give rise to accumulation of fatty acids, ketone bodies and amino acids, and to formation of certain physiologically active substances which play a very important part in the subsequent defensive physiological phenomena.

Accumulation of acid metabolites results in acidosis. At first, acidosis is compensated thanks to alkali reserves of the blood and tissue fluid. Besides, part of these substances is removed from the focus of inflammation by the blood and lymph flow. But then exhaustion of the alkali reserves and insufficient outflow of blood from the inflamed area result in increase of free hydrogen ions concentration in the tissues and development of uncompensated acidosis.

The more acute the course of the inflammatory process, the more marked is the acidosis: in chronic inflammation pH=7.1 - 6.6, in acute purulent inflammation- 6.5 - 5.4. In the center of the focus hydrogen ions concentration may increase 50- fold. Development of inflammation also results in increase of acidosis.

Hydrogen ions concentration and the osmotic pressure gradually decrease towards the periphery of the inflammatory focus (towards normal tissues).

In exudative inflammation, thanks to autolysis and accumulation of alkaline products of protein disintegration (ammonia) in the exudate, its reaction may become alkaline (surrounding tissues reaction will be acid).

Owing to intensified dissociation of salts in acid medium, in the focus of inflammation content of other ions also increases, the proportions of electrolytes change. For instance, the concentration of potassium ions and K/Ca coefficient increase. As a result of accumulation of ions and products of tissue disintegration (splitting of large molecules into numerous small molecules) the osmotic pressure in the inflamed tissue rises (for instance,19 atm instead of the normal 8 atm).The oncotic pressure of tissue colloids also rises. Like acidosis, these also gradually decrease from the center to periphery of the inflammatory focus.

So, in the focus of inflammation accumulation of ions (especially increase of hydrogen ions concentration) and increase in oncotic pressure of tissue colloids is observed. As a result of trophic tissue changes, these disturbances in their turn influence the extend of the subsequent changes developing in the cells of the inflamed tissue. In the altered physicochemical environment the colloidal structure of the cells is disturbed with phenomema ranging from swelling to necrobiosis and even necrosis.

Mediators of inflammation influence vascular permeability and tension, as well as activity of leukocytes. So, they play an important part in the course of the inflammatory reactions.

Practically all mediators of inflammation are also modulators, that is, they are able to strengthen or weaken expressiveness of inflammatory symptoms.

The sources of some mediators (kinins, kallikrein, Hageman factor, complement, etc.) are blood plasma proteins, whereas others are liberated from altered cells, especially from mast cells, basophils and thrombocytes (histamine, serotonin), neutrophils, macrophages, monocytes and lymphocytes (leukokines, lymphokines, monokines).

At present about 30 types of mediators of inflammation are known. Actually all of them influence the vessels of microcirculatory system as well as activity of leukocytes once way or another. Therefore, in the classification of mediators their prevailing actions are taken into account.

According to the pathophysiological action mechanism of the mediators of inflammation they are divided into 2 groups:

1. the mediators which influence mainly vascular wall tension and permeability;
2. the mediators which influence mainly the functional properties of leukocytes.

Mediators which influence vascular wall tension and permeability, are the following:

1. Biogenic amines- histamine, serotonin, etc.

Histamine is of great importance in the pathogenesis of inflammatory reactions in human organism. It decreases the vascular tension and increases permeability, and this way makes difficult outflow of the blood from the focus of inflammation.

2. Kinins- bradykinin, kallidin, etc. Bradykinin easily passes from tissues into blood vessels and in the opposite direction, dilates blood vessels, decreases arterial pressure, increases vascular permeability thrice stronger than histamine. It is the strongest agent causing pain. But this property of bradykinin is manifested only in the presence of serotonin. Therefore, when it is injected into normal tissues, the pain sensation is weak, whereas in congested areas bradykinin causes strong sensation of pain.

In the formation of bradykinin great is the role of Hageman factor. So, this factor plays decisive part in the pathogenesis of the inflammatory reactions(participates in the process of kininogenesis, activation of fibrinolysis system, contact phase of blood coagulation.).

1. Plasmin (fibrinolysin) is formed as a result of activation of plasminogen (under the influence of specific activators and Hageman factor). It partipicates in the mechanism of inflammatory processes (accelerates kininogenesis. Fibrinolysin plays an important part in absorption of fibrinous exudate in lungs (croupous pneumonia), intestine (dysentery) and so on.
2. Permeability factor (globulin) activates kallikrein and in this way accelerates formation of bradykinin. This factor is activated when it gets in touch with damaged endothelial wall or under the influence of acidosis in the focus of inflammation.
3. Prostaglandins-especially prostaglandins E1 and E2 take active part in the pathogenesis of inflammation. They dilate vessels, increase vascular permeability, stimulate lymph flow.
4. Neuromediators(neurotransmitters) – epinephrine (adrenalin) and norepinephrine increse tension of arterioles and decrease vascular permeability, that is, their action in the focus of inflammation is opposite to that of kinins and histamine;acetylcholine dilates vessels.

Mediators which influence functional activity of leukocytes, are the following:

1. Complement system (C3a, C5a, etc.) and its physiologically active by – products increase vascular permeability, chemotaxis of polymorphonuclear leukocytes and macrophages, accelerate liberation of lysosomic enzymes, strengthen phagocytosis. They also damage the cell membrane, cause osmotic lysis and ruin of cells.

In the period of complement’s activation a number of mediators of inflammation are formed. One of them is chemotactic substance which causes accumulation of leukocytes in the focus of inflammation and formation of cellular infiltration.

2. Leukotrienes - LTB4, LTC4, LTD4,LTE4. LTB4 is synthesized in the neutrophils and eosinophils which are accumulated in the focus of inflammation, and stimulates their activity. It causes accumulation of leukocytes in the inflamed area and increases vascular permeability. LTC4 , LTD4 and LTE4 are in the slow reacting substance of anaphylaxis whose physiological activity is connected with leukotrienes.

Frequently around the inflamed area edema develops. For instance, edema of soft tissues of the face in inflammation of the tissues of dental alveoli and pulp (alveolar abscess).

Increase of capillary permeability under the influence of biologically active substances (histamine, bradykinin, etc.) play an important part in the mechanism of the inflammatory edema. As a result of delay of blood and lymph outflow from the inflamed area blood plasma and lymph pass into the tissues, and edema develops.

Inflammatory edema has certain defensive significance. Proteins of tranaudate bind the toxic substances of the inflamed tissues, neutralize the toxic products of decomposition of tissues. This impedes passage of those substances from the focus of inflammation into general circulation and prevents their spreading in the organism.

Mediators of inflammation prepare the ground for the next stage of the inflammation. Development and character of the local circulatory disorders are closely connected with the action of mediators.

The following successive (to some extend) changes take place at the third stage of the inflammation:

1. Vascular reactions of the microcirculatory system.
2. Changes in the rheologic properties of the blood.
3. Increase of vascular permeability in the microcirculatory system.
4. Exudation of the substances forming part of the blood plasma.
5. Emigration of the cellular elements of the blood.
6. Phagocytosis.
7. Formation of exudate and cellular infiltrate .

*Vascular reactions of the microcirculatory system consist of 4 stages:*

1. *brief spasm of arterioles;*
2. *arterial hyperemia;*
3. *venous hyperemia;*
4. *stasis*.

The spasm of arterioles and pallor of the injured organ or tissue result from stimulation of vasoconstrictor nerves by the agent causing inflammation. But influence of the initial agent is momentary, and adrenalin is broken down by the enzyme monoamine oxidase. Therefore, this phenomenon rapidly (from 10-20 seconds to several minutes) disappears, and it is not always possible to observe it.

The spasm is followed by dilatation of arterioles and capillaries; more blood is brought to the inflamed part, that is, arterial hyperemia begins. One of the main causes of vascular dilatation in the focus of inflammation is the reflex effect of the damaging agent. Besides, a number of physicochemical and chemical changes in the inflamed focus (increased concentration of hydrogen ions and potassium ions), some metabolic products and mediators that are formed as a result of injury (histamine, kinins, acetylcholine, nucleotides, prostaglandins, etc.) cause vasodilative action. Usually dilatation of the arterioles follows their constriction, but may occur at once owing to rapid paralysis of the vasoconstrictors and excitation of the vasodilators.

As a result of dilatation of arterioles and increased inflow of the blood into inflamed area, blood pressure in capillaries and veins increase, then circulation rate gradually decreases, vessels in the venous part of the microcirculatory system dilate. The dilated vessels become engorged with blood and the arterial hyperemia is replaced by the venous hyperemia.

Venous hyperemia is connected with the changes in the blood, vascular wall and tissues:

1) in the blood- approach of leukocytes to the vascular wall(marginal position of leukocytes), swelling of erythrocytes, concentration of the blood, formation of microaggregates and microthrombi, acidosis;

2) in the vascular wall-paralysis of neuromuscular apparatus(decrease of vascular tension, swelling of the endothelial cells and disturbance of the structure of veins;

3) in the tissues- formation of infiltrates, swelling of tissues, damaging of the small connective tissue fibers surrounding the veins and capillaries.

One of important factors responsible for slowing of the blood current is discrepancy between the increase in the cross- section of the vascular bed and that in the volume of the circulating blood.

Frequently in the microcirculatory system of the inflamed area pendular movements of the blood are observed, that is, during systole the blood moves to the venous system and during diastole- to the arterial system. At last, blood flow comes to complete standstill, and stasis sets in.

At the phase of stasis all consequences of the cessation of the blood flow are observed: disturbances in the physicochemical properties of the vascular walls, formation of microthrombi, hemorrhages, etc. Number of the aggregated erythrocytes increase, the phenomenon of sludge occurs.

So, changes in the rheologic properties of the blood become marked.

One of the main factors in the pathogenesis of the inflammation is increase of vascular permeability in the microcirculatory system. This is caused by mediators of inflammation, injury of lysosomal membranes (liberation of enzymes), changes in the ultrastructure of cells. Dilatation of the vessels is in itself conducive to increased permeability of vascular walls.

All the changes that are observed in the course of inflammation depend on the extend of increase of vascular wall permeability. Exudation and emigration, formation of exudate and inflammatory cellular infiltrate are connected precisely with the increased vascular permeability.

Exudation is passage of the fluid part of the blood and blood cells through the walls of the vessels into the inflamed tissues, interstitial space and cavities of the body .

The fluid that passes from the vessels into the tissues or cavities of the body in inflammation, is called exudate. Emigration, i.e, passage of leukocytes from the vessels into the inflamed tissues, is one of manifestations of the exudation.

Exudation is caused by the :

1) increased vascular permeability in the microcirculatory system;

2) increased blood pressure(infiltration pressure) in the blood vessels supplying the inflamed area;

3) increased oncotic pressure in the inflamed tissues.

Plasma and cellular elements go out of the vascular wall by two ways:

1.Intercellular way- when the vessels are dilated, fissures between the endothelial cells increase, water, substances that are dissolved in the water and neutrophils go out through these spaces.

2. Transcellular way- elements of blood go out through the cells:

a) different factors(increased intravascular hydrostatic pressure, histamine,serotonin, bradykinin, prostaglandins,permeability factor)enlarge pores in membranes of the endothelial cells, and elements of blood easily pass through microcanals connected with these pores.

b) micropinocytosis- endothelial cells swallow the fluid particles and take them through the protoplasm.

Leukocytes begin to go out of the vascular wall in the phase of the arterial hyperemia, but their emigration is accelerated in the phase of the venous hyperemia. Three periods are distinguished in the emigration of the leukocytes:

1. marginal position of leukocytes- approach of leukocytes to the endothelial coat and adhesion to it;
2. passage of leukocytes through the endothelial coat;
3. movement of leukocytes in the intercellular space of the focus of inflammation.

Adhesion of leukocytes to the endothelial coat of the vascular wall is explained as follows. When the blood stream is slowed down leukocytes join with the fibrinous fibers covering the inner surface of capillaries. Besides, in the process of emigration leukocites lose their negative charge which is neutralized by calcium ions, while endothelial cells carry negative charge. Calcium bridges are formed between the leukocytes and endothelial cells. Leukocytes are delayed in the vascular wall from several minutes to half an hour and go out of the vascular wall in several minutes to half an hour and go out of the vascular wall in several minutes.

Depending on the mechanism of passage of different types of leukocytes through the endothelial cells the rate of their movement is also different. In the first place polymorphonuclear granulocytes (neutrophils and eosinophils) pass into the focus of inflammation, then monocytes and finally- lymphocytes. Because granulocytes pass into the intercellular space through the fissures between the endothelial cells. Their pseudopodia enter between the endothelial cells, and then the protoplasm and nucleus go out.

But mononuclear cells(monocytes and lymphocytes)at first enter the endothelial cells, move in them in the form of vacuoles and go out from the opposite side.

Directional movement of leukocytes to the focus of inflammation is explained by the phenomenon of positive chemotaxis. Calcium and magnesium ions take part in the process of chemotaxis.The substances accelerating movement of leukocytes by the way of chemotaxis are divided into two groups:

1) cytotaxins- attract leukocytes directly: some activated components of the complement system (C3a, C5a, etc.), kallikrein, denatured proteins, bacterial toxins, peptones,some products of leukocytes desintegration(lymphokines), leukotrienes, etc.;

2) cytotaxigens- do not cause chemotaxis immediately but convert some substances into cytotaxins: trypsin, fibrinolysin, collagenase, antigen- antibody complex, starch, glycogen, bacterial lipopolysaccharides, immunoglobulins (IgA, IgM), etc.

After passing into intercellular space, the leukocytes move in the tissues from several hours to several days.

In the process of inflammation erythrocytes also pass from vessels into intercellular space. Erythrodiapedesis is marked especially when the vascular wall permeability is sharply increased(anthrax, plague, etc.).

Emigrated leukocytes participate in the process of decontamination by the way of phagocytosis of large- molecular substances which are formed in the tissues under the influence of factors causing inflammation(microorganisms, foreign bodies, cell injury, etc.).The process of exudation ends with formation of exudate and inflammatory infiltrate.

Exudate consists of fluid part, cellular elements and products of tissue disintegration. Just accumulation of exudate in the focus of inflammation results in swelling of tissues, squeezing of nerve ceptors and sensation of pain, dysfunction of organs and tissues.

Quality and quantity of exudate depends on the type of agent causing inflammation and anatomic – physiological properties of the damaged tissue. In the composition of exudate components of blood plasma or cellular elements predominate, and frequently microorganisms are found . Exudates differ from one another by the amount of proteins and cellular elements (neutrophils, lymphocytes or monocytes, as well as erythrocytes).

Exudate differs from transudate (dropsical fluid ) by its composition. For instance, exudate contains much proteins (albumen - globulin ratio-0.5-1), its specific mass is1.018 or more and active reaction is acid (pH<7). Transudate contains less proteins (albumen - globulin ratio-2-4), its specific mass is 1.006- 1.013 and pH is equal to that of the blood. Exudate frequently coagulates, whereas transudate does not coagulate. Although the serous exudate contains lesser cellular elements, but it also differs from the transudate by its main properties.

Accumulation of the cells of exudate in tissues leads to formation of cellular infiltrate which may contain hematogenous as well as histiogenous cellular elements. Most of neutrophils and monocytes in the infiltrate perish in 3-5 days. Damaged leukocytes in the infiltrate are called “suppurative bodies”.

Changes in the rheologic properties of the blood are observed in all stages of the inflammation. But with the development of the process these changes bacome more marked.

As a result of exudation the blood thickens. Acidosis causes swelling of blood cells and endothelial cells. Damage to endothelial cells, thrombocytes and other blood cells leads to increase of blood coagulability. Formation of thrombi makes difficult outflow of blood by veins. At the same time, this leads to occlusion of lymphatic viae and disturbance in the lymph flow. Frequently the swollen erythrocytes form microaggregates in the vessels which occlude the small vessels.

The process of inflammation ends with proliferation of cells and recovery of the damaged tissues. Metabolic products in tissues stimulate the proliferation. In the onset of this process a great role belongs to the tissue hypoxia and physicochemical changes connected with it.

Usually proliferation does not begin simultaneously in all parts of the focus of inflammation. At the initial stage of the inflammation the physicochemical changes in the central zone of the damaged area accelerate development of dystrophic processes, while at the same time low acidity and slight changes in the colloid osmotic pressure in the peripheral zones of the inflammatory focus stimulate development of the proliferation.

Mesenchymal, adventitial, endothelial cells, lymphocytes and monocytes take part in the process of proliferation, whereas polymorphocellular granulocytes (neutrophils and eosinophils ) perish before the proliferation begins.

Monocytes and tissue macrophages (histiocytes) swallow and dissolve the damaged cells, small thrombi and foreign bodies; the process of intracellular digestion is accelerated. The area of inflammation is gradually cleaned from the necrotic cells and tissues, and mesenchymal cells begin to multiply.

At the stage of proliferation mesenchymal (cambial) cells are converted into fibroblasts; from B lymphocytes plasma cells and labrocytes are formed; monocytes develop and change into histiocytes and macrophages; from macrophages epithelioid cells and from them-giant cells (Pirogov-Langhans cells) are formed. In the fibroblasts rapidly tropocollagen is synthesized; this protein is the initial material for formation of collagen. At the same time part of fibroblasts is turned into fibrocytes, that is, mature cells of the connective tissue. Argyrophile and collagenous fibers which are products of activity of fibroblasts and fibrocytes, restrict the focus of inflammation and eliminate the tissue defect. At the proliferative stage of inflammation the anabolic processes are accelerated. Proliferation is closely connected with regeneration of the damaged tissues. At the end of this process in the focus of inflammation connective tissue develops, the new blood vessels and in some cases- the specific elements of the damaged tissues are formed.

If the damaged area of the tissue is not very large, the inflammation ends with complete regeneration, while the inflammation of large areas usually causes cicatrization (as a result of development of the connective tissue). In some cases scarry tissue deforms organs and tissues and causes dysfunction (for instance, valvular defects as a result of rheumatic endocarditis).

The local signs, that is, internal and external (clinical) cardinal signs and general signs of inflammation are distinguished.

The internal cardinal signs or main components of inflammation are: alteration, microcirculatory disorders (including exudation and emigration) and proliferation.

The external (clinical) cardinal signs of inflammation are: redness (rubor), swelling (tumor), heat (calor), pain (dolor) and dysfunction (functio laesa).

Redness is due to dilatation of microcirculatory vessels (hyperemia) in the focus of inflammtion and decrease of circulation rate. At first the damaged area is tinged scarlet(arterial hyperemia), then becomes cyanotic(venous hyperemia).

Swelling is connected with inflow of blood into the vessels of the damaged area, formation of infiltrate, development of perifocal edema, and then-proliferation of the cells.

Heat is due to inflow of arterial blood into the focus of inflammation and acceleration of metabolism.

Pain is a result of irritation of the sensory nerve endings by acids, potassium ions, physiologically active substances (kinins, histamine, serotonin) and mechanical action of exudate and infiltrate. Throbbing pain results from mechanical irritation of nerve endings connected with formation of capillary pulse when arterioles are dilated (in pulpitis, panaritium and other pyo –inflammatory processes).

Dysfunction may include only the damaged organ or be general (when the vital organs are inflamed).

All the complex of these signs is mainly characteristic of acute inflammation of the skin and mucous membranes (abscessus, burns).In a number of cases of inflammation, especially that of internal organs, some of signs are either feebly marked or totally absent. For instance, in the liver, kidneys and heart the inflammatory, redness is often camouflaged by the organ’s normal colour; in chronic inflammation there may be no swelling, redness, heat or pain(in hepatocirrhosis, granular kidney, etc.).

The general signs of inflammation are the following:

1. Fever - is caused by pyrogenic substances which are formed in the inflammatory focus.

2. Leukocytosis- is resulted from activation of leukopoiesis and redistribution of leukocytes (stimulation of sympathoadrenal system, influence of bacterial toxins, pruducts of tissue decomposition, mediators of inflammation). Rarely (for example,in inflammation of viral origin) leukopenia occurs.

3. Increase of ESR (erythrocyte sedimantation rate)-as a result of decrease of negative charge of erythrocytes, increase of blood viscosity, agglomeration of erythrocytes, changes in blood protein composition, rise of temperature.

4. Change of protein “profile” of the blood-in the acute process “proteins of the acute phase “ of the inflammation (C-reactive protein, ceruloplasmin, haptoglobin, complement’s components, etc.) are accumulated in the blood; in the chronic inflammation blood content of alpha- and espesilly gamma- globulins is increased.

1. Changes in fermental composition of the blood-increase of activity of transaminases, hyaluronidase, thrombokinase, etc.
2. Changes in blood content of hormones- increase of concentration of catecholamines, corticosteroids.
3. Changes in the immunogenic reactivity and allergization of the organism.
4. Intoxication of the organism and sepsis.
5. Formation of pathological reflexes (development of stenocardia in cholecystitis, of cardiac arrhythmia in appendicitis).

The etiologic agent, rate of development of the process and character of the tissue reactions are taken into consideration in the classification of inflammation.

According to the type of the etiologic agent:

1. Specific inflammation- is manifested, besides general signs of the inflammation, by some signs characteristic of only given agent (tuberculosis, syphilis, lepra, anthrax, etc.).
2. Non-specific (commonplace) inflammation- inflammatory prcesses that are caused by different (biological,physical, chemical) factors, but are like by their clinical signs.

According to the course of the inflammatory process:

1. acute
2. subacute
3. chronic.

According to the clinical and morphological signs:

1. Alterative inflammation-tissue injury (dystrophy, necrosis) predominates. Since cellular elements are damaged more, it is called also parenchymatous inflammation.
2. Exudative (exudative-infiltrative) inflammation-acute vascular reactions, exudation and emigration of leukocytes predominate. According to the properties of the exudate several types of the exudative inflammation are distinguished: serous, catarrhal, fibrinous, hemorrhagic, purulent, putrid, mixed.
3. Proliferative (productive) inflammation-is characterized by the rapid reproduction of cells and formation of new tissue elements (usually in chronic infectious processes, tuberculosis, syphilis, etc.).

Serous inflammation is observed in the serous cavities of the organism, membrane, meninges, sometimes- in the internal organs. Serous exudate is a semi-transparent yellowish fluid of flow specific gravity (1.015-1.020), containing protein (3-6%) and a small number of cells.

Catarrhal inflammation develops frequently in the mucous membrane of the respiratory tracts, esophagus, stomach , intestine. Catarrhal exudate contains a large amount of mucus.

Fibrinous inflammation is observed often in the mucous and serous membranes, but rarely- in the internal layers of the organs. Fibrinous exudate contains a large amount of fibrinogen and therefore, coagulates. Fibrinous inflammation is caused by pneumococci, bacteria of diphtheria and dysentery. In the croupous inflammation (in trachea, pericardium, pleura) the fibrinous exudate freely covers the surface of the mucosa as a grey membrane and can easily be removed without any injury to the mucosa, whereas in the diphtheritic inflammation (in dysentery, or the fauces and tonsils in diphtheria) the fibrinous exudate impregnates the mucosa which undergoes necrobiotic changes; removal of the fibrinous membrane exposes the ulcerated surface.

Hemorrhagic exudate contains a large number of erythrocytes (in anthrax, plague, etc.).

Purulent inflammation is caused frequently by the pyogenic microorganisms (staphylococci, streptococci, gonococci, meningococci), typhoid and pyocyaneous bacilli, rarely-by pneumococci, as well as some chemical substances (croton oil, turpentine, war gases). Purulent exudate is protein- containing fluid with an enormous number of leukocytes, mainly neutrophils, mostly destroyed by the effects of toxic substances of harmful agents. Its specific mass is higher (1.020-1.040) than that of other exudates. It contains a large number of enzymes, lactic acid, peptons, polypeptides, amino acids, cholesterol, deoxyribonucleoproteids, DNA, etc.

Putrid (ichorous or gangrenous) inflammation is caused by the putrefactive bacteria.

Mixed inflammation develops as a result of complication of the basic inflammatory process by the secondary infection (in the organisms with sharply decreased defensive functions).In the mixed inflammation serofibrinous, serohemorrhagic, seropurulent or pyofibrinous exudates are found.

The character of the exudate depends on the harmful agent, duration and intensity of its action , site of inflammation. In the course of inflammation one form of exudate may change to another.

The changes caused by the inlammatory process in the organism depend mainly on the following factors:

1) strength of the agent causing the inflammation;

2) duration of the agent’s action;

3) the organism’s reactivity;

4) functional- morphological properties of the damaged organ.

Usually the strong agents acting during a short time cause acute inflammatory process, and the weak agents acting during a long time- chronic inflammation. The same agent may cause different pathological processes in different tissues depending on the innervation of the organ, properties of its blood supply, development of connective tissue, intensity of metabolism.

Though a local reaction of tissues to the injury, inflammation affects the whole organism and causes a number of important changes in its general state. The local and general phenomena of inflammation are closely interconnected. Usually inflammatory processes are accompanied by above mentioned general signs - fever, leukocytosis, increase of ESR, changes in the metabolism of proteins and carbohydrates, etc. These changes influence the organism’s reactivity (including the immune reactivity). The general manifestations of inflammation are connected with spreading of biologically active substances, toxins, bacteria and products of their activity from the damaged areas all over the organism. Besides, the inflammatory process may exert its general action by the reflex way.

According to the character of the organism’s reactivity the following types of the inflammatory processes are distinguished:

1. Normergic inflammation- is a usual, most common inflammatory reaction in a normal organism.

2. Hyperergic inflammation-is excessively strong reaction of sensitized organism to the action of substances of antigenic nature (Arthus’ phenomenon, Pirquet reaction, etc.) or usual stimuli. Acute rheumatism, croupous pneumonia , sclerodermia are accompanied by the signs of hyperergic inflammation.

3. Hypoergic inflammation- is characterized by mild inflammatory phenomena. It develops in an organism possessing increased resistance to the action of the stimulus (for instance, in an organism immune to diphtheria).Such altered reactivity of the tissue due to the immune state of the organism is called positive hypo or anergy. Negative hypo-or anergy is observed in an emaciated organism as a result of its decreased reactive capacity (in patients with malignant tumors or in longstarving people).

Origination and development of the inflammatory reactions depend also on the functional state of the nervous system. Reflex reactions play an important part in the appearance of inflammation. For instance, resection of the afferent part of the reflex arc or administration of anesthetics capable of blocking receptor structures perceptibly weakens and sometimes stops the inflammatory process. Anesthesia of the tissue induced before the inflammation has an even stronger effect.

Inflammatory processes developing at symmetrical sites are explained by purely reflex reasons. For instance, the inflammation produced by administration of tuberculin into the skin of one limb sometimes causes symmetrical inflammation of the other limb.

Various structures of the central nervous system participate in the mechanism of inflammation. For example, it is possible to alter the functional state of the central nervous system(experimental neurosis)and produce conditioned reflex leukocytosis and phagocytosis. Phenomena of inflammation were observed on the human skin as a response to hypnotic suggestion that the subject’s body was being touched with something hot.

The vegetative nervous system also plays an important part in the course of the inflammatory reactions. Hyperfunction of the sympathetic nervous system inhibits the development of inflammation and its hypofunction tends to stimulate the process.

The more complex the organism and the more differantiated its nervous system, the more clearly and fully marked its inflammatory reaction, especially the defence physiological phenomena(emigration, phagocytosis, proliferation) are.

Participation of the endocrine glands in the development of inflammation is closely connected with the function of the nervous system. The same etiologic agent causes more strong inflammatory reaction in patients affected with exophthalmic goitre than in those with myxedema. Adrenocorticotropic hormone inhibits the inflammatory reaction by stimulating secretion of glucocorticoids (hydrocortisone and cortisone) whereas somatotropic hormone stimulates it directly or through the mineralocorticoids (desoxycorticosterone, aldosterone).

As for nomenclature of the inflammation, to designate most of the inflammatory processes it is customary to add the Latin suffix “itis” to the Greek or Latin name of the affected organ or tissue, as peritonitis (inflammation of the peritoneum), arthritis (inflammation of joint), dermatitis (inflammation of the skin), etc. By the same terms are designated the diseases whose main symptom consists of the inflammation of some organ (appendicitis, gastritis, hepatitis, colitis, etc.).

Inflammation of some organs has been given a special designation, as pneumonia (inflammation of the lungs), angina (inflammation of the fauces), nasal cold (inflammation of nasal mucous membrane), though some of them may be called also according to the general rule (pharyngitis, tonsillitis, rhinitis, etc.).

Inflammatory processes in the internal layers of the cavitary or tubular organs are designated by the prefix “endo” (endocarditis, endometritis, endovasculitis), in the middle layer- by the prefix”meso” (mesaortitis), in the tissues surrounding the organ-by the prefix”para” (parametritis, paranephritis).

The cavity filled with pus and formed by mortification and liquefation of tissue in the focus of purulent inflammation is clled abscess. Abscess is limited purulent inflammatory process in tissues (hepatic abscess, pulmonary abscess). Usually pus subsequently makes its way from the abscesses either to the exterior or into internal cavities. Accumulation of pus in a closed cavity is called empyema (empyema of the pleural cavity, the gallbladder).Purulent infiltration spreading through loose connective tissue (subcutaneous, interstitial)and affecting large sections of tissue is called phlegmon.

Outcome of inflammation may be as following:

1) restitution ad integram- return to the normal state with restoration of the anatomic and functional properties of the tissue as a result of recovery of its specific elements;

2) formation of scar tissue which may not affect the functional properties of the organs (small scars on the skin)or may, if extensively developed, cause displacement of organs (pleurisy, pericarditis) and functional disturbances (scars in the central nervous system);

3) destruction of tissue (sometimes of the organism), depending on the character of the inflammation and the site of development.

Two interconnected and frequently inseparable processes must be distinguished in inflammation: on the one hard, the pathological process proper-damage to the tissue in the form of dystrophy, necrobiosis or necrosis, and , on the other hand, the defensive- physiological, restorative process in the form of exudation, phagocytosis and tissue proliferation. It is precisely the simultaneous operation of both processes that is particularly characteristic of inflammation.

The process of alteration in the focus of inflammation causes different disturbances in the activity of tissues and organs. For instance, in the inflammation of joints movements become painful and limited. Hepatitis causes disturbances in the numerous functions of the liver which lead to different metabolic disorders, etc. The exudate accumulated in pulmonary alveoli in pneumonia makes the general state of the organism more grave. Gaseous exchange in the organism is disturbed. The bacteria that are swallowed by phagocytes, but are not digested, may spread to other areas of the organism (incomplete phagocytosis).

At the same time, inflammation is of adaptative significance for the organism. It prevents spreading of the pathogenic agent in the organism and increases ability of tissues to regenerate. Weakening of the blood flow in the focus of inflammation and perifocal edema delay spreading of bacteria and toxins in the organism. This is barrier function of inflammation. Connective tissue cells(macrophages, histiocytes) kill pathogenic microorganisms by the way of phagocytosis and accelerate development of the cicatricial tissue by the way of synthesis of collagenous protein. The granulation tissue formed by them also prevents spreading of the infection in the organism.

As a result of proliferation of lymphocytes and plasma cells in the focus of inflammation, formation of antibodies is accelerated, that is , immunity of the organism is increased. The ability of the organism to phagocytosis is increased.

***Fever is general adaptive reaction of warm-blooded animals and human organism which consists in elevation of body temperature by formation of heat in organism as a result of changes (reset) in the thermoregulation mechanisms under the action of non-infectious and most frequently infectious agents.***

Unlike hyperthermia which occurs only under the influence of elevated temperature of the external environment, fever occurs regardless of the temperature of the external environment and may appear under usual temperature conditions.

Fever (febris) is one of the ancient terms used in the medicine. Its main external signs (fit of shivering and then sharp rise in body temperature) were known in antiquity.

Fever was regarded as independent nosologic unit. This comprehension of fever is reflected in the names of such diseases as yellow fever, Q fever, pappataci fever, etc.

But at the same time the idea about the fever as a typical pathological process was formed, that is, fever was regarded as one of constant symptoms of different diseases, and first of all, of infectious diseases.

Biologically active substances causing increase of body temperature are called the pyrogenic (Gr. pyr- fire, heat; genes-generating) substances. Phylogenetically fever appeared after the inflammation. It is observed only in the animals with well developed mechanisms of thermoregulation. Higher the level of the evolutional development of the homoiothermal animals, more sensitive they are to action of the pyrogenic substances.

As for ontogenesis, in new- born children the mechanisms of thermoregulation are weak (especially heat emission), and their organism is unstable homoiothermal. Their body is easily cooled and warmed depending on the changes in the temperature of the external environment. Pneumonia in infant during the first 3-4 months of his life proceeds with weak feverish reaction; after 4 months it is accompanied by the high body temperature.

Fever is one of the main sings of different dieases which thoroughly differ by their etiology. According to the etiologic agent infectious and noninfectious fevers are distinguished.

Infectious fevers are the most common. They occur as a result of the action of bacteria, viruses, protozoa, pathogenic fungi, their toxins and waste products, as well as that of pyrogenic substances obtained from microbial bodies or present in products of bacterial origin and tissue disintegration, for example, in pus, extracts from foci of inflammation, putrescent tissues (nucleoproteins, lipopolysaccharides, etc.).

Noninfectious fevers occur in aseptic inflammatory processes resulting from mechanical, physical, chemical injuries of tissues, in tissue necrosis connected with circulatory disorders (myocardial infarction), etc. In those cases fever occurs as a result of emigration of leukocytes into the focus of inflammation, where the leukocytes are activated and secrete pyrogen substances.

So, though different from etiologic point of view, infectious and noninfectious fevers are alike by their pathogenesis.

Some hormonal disorders, emotional stress, reactions of hysteria, drugs cause rise of body temperature. But in the pathogenesis of such fever pyrogenic substances do not participate. The most frequent types of noninfectious fevers are protein fever, salt fever, drug fever, neurogenic fever.

Protein fever may be resulted from action of exogenous and endogenous proteins.

Exogenous protein fever is evoked by parenteral administration of solutions containing proteins (milk) or large- molecular products of incomplete hydrolysis of proteins (albumoses, peptones). Endogenous protein fever occurs as a result of denaturation of organism’s own proteins (in interstitial hemorrhages, aseptic necroses, bone fractures hemolysis, malignant tumors). It also results from action of toxic products of albuminous nature absorbed through the altered intestinal mucosa or from hypofunction of the excretory organs which normally eliminate these products.

Salt fever is produced by injection of hypertonic sodium chloride solution. It is a result of osmotic disturbances, destructive changes and consequent passage of pyrogenic substances into the blood.

Drug fever results from injections of adrenalin, phenamine, thyroxin, cocaine, B- tetrahydronaphthylamine, dinitrophenol, nicotine, caffeine. Some of them (adrenalin, phenamine, etc.) are sympathicotropic and excite the heat-regulating center, others(dinitrophenol)directly influence tissue metabolism and cause excessive heat production. Unlike the true fever, the level of the drug fever depends on the temperature of the external environment.

Neurogenic fevers differ from the true feverish reactions by their mechanism of development. They are caused by injuries and contusions of the brain, heat puncture, psychic trauma, tumors of the diencephalon, hemorrhages into the third ventricle and reflex stimulation of the heat- regulating center( in renal or hepatic colic).

Under natural conditions above- mentioned factors are frequently combined. For instance, any infectious fever is in its pathogenesis also a protein fever. Dysfunction of the nervous system is observed in the mechanism of any fever.

The pyrogenic substances are divided into two groups;

1) exogenous( products of vital activity or disintegration of microorganisms);

2) endogenous( formed in the organism under the influence of various etiologic, mainly infectious agents).

The most of the pathogenic and some nonpathogenic bacteria, a number of viruses and yeast fungi possess pyrogenic activity. Pyrogenic action of bacteria does not depend on their pathogenicity and toxicity.

Refined bacterial pyrogens are large-molecular organic compounds from the group of lipopolysaccharides which do not lose their pyrogenic properties at 140o C. The small doses (1mkg/kg) of pyrogenic substances increase the body temperature markedly. Pyrogenal, pyrexal and other lipopolysaccharides are used in the experimental and clinical medicine. The pyrogenic substances were not found in viruses, rickettsia and spirochetes. Evidently, they stimulate formation of the endogenous pyrogenic substances by the way of damaging the cells and tissues.

There are no pyrogenic substances in the healthy organism. The endogenous pyrogenic substances are synthesized during infectious diseases and aseptic injuries in the granulocytes and monocytes, pulmonary macrophages, mononuclear cells of the spleen and lymphatic nodes, Kupffer cells of the liver, macrophages in the peritoneal exudate. Neutrophils and macrophages are activated in the period of pinocytosis of bacterial lipopolysaccharides in the focus of inflammation, phagocytosis of bacteria and their particles, viruses, perished leukocytes, products of the tissue disintegration, etc.

Endogenous pyrogens are formed in the blood of the animals 20- 30 minutes later after the injection of the bacterial pyrogen substance.

The properties of the pyrogenic substance synthesized in neutrophils are well studied. This is thermolabile albuminous substhance.Inhibitors of glycolysis decrease synthesis of leukocytic pyrogens; blockade of the RNA’s synthesis has the same effect.

Formation of endogenous pyrogenic substanses is accelerated, besides infectious factors and inflammatory exudate, by the antigen-antibody complexes. That is why in the sensitized organism infectious diseases are accompanied by the high feverish reaction.

The latent period of fever caused by exogenous pyrogenic substance depends on its dose and site of penetration into organism. For instance, when injected intravenously, bacterial vaccines increase body temperature in 15-40 minutes, whereas during subcutaneous injection the latent period is twice longer. To produce fever in rabbit and dog suffice to inject several thousand times less pyrogenic substance into the ventricles of brain than intravenouly.

Repeated administration of bacterial pyrogenic substances into the organism causes formation of tolerance against their action, and to produce fever higher doses are required. But endogenous pyrogens do not cause tolerance and evoke fever even in the organisms that are insensitive to the exogenous pyrogens.

In agranulocytosis in human organism or in conditions of blockade of the mononuclear phagocytic system by the chemical substances in animals the usual doses of the bacterial pyrogenic substances do not cause fever.

Activation of leukocytes is the first stage of the synthesis and secretion of pyrogenic substances. In the experiments in vitro duration of this stage is 1-2 hours. Formation of the pyrogenic substances (the second stage) lasts 16-18 hours in granulocytes and up to 35 hours in monocytes.

The principal action mechanism of pyrogenic substances is connected with changing of the interrelation between the processes of excitation and inhibition in the thermoregulation centers. Pyrogens strengthen the process of excitation in the cold receptors and inhibition-in the warm receptors. As a result, in the thermoregulation centers the normal temperature of the organism is perceived as low temperature.

Thus, the action mechanism of the pyrogenic substances on the organism is the following.

The exogenous pyrogenic subtances activate monocytes and granulocytes where the endogenous (leukocytic) pyrogenic substances are synthesized. The endogenous pyrogens, in their turn, cause rise of body temperature by the way of increasing the amount of cyclic adenosine monophosphate (AMP) in the neurons of the thermoregulation centers. This is achieved directly or by the way of acceleration of the synthesis of prostaglandin E1 in the neurons. Since prostaglandin E1 is inhibitor of the enzyme phosphodiesterase which breaks down the cyclic AMP, the latter is accumulated in the neurons. Accumulation of cyclic AMP leads to decreased metabolism (O2 consumption), accumulation of the metabolic products, changes in the ionic balance, and finally- to increased excitability of the cold – sensitive neurons and decreased excitability of the warm sensitive neurons. This causes increased heat production and limitation of heat loss. Body temperature rises - the first stage of fever. At the second stage of the fever sensitivity of the central thermoregulation receptors to the cold and warm approaches the norm, and mechanisms of thermoregulation begin to function on the new (heightened) level. The third stage of the fever (decrease of body temperature) is based on the changes which are opposite to those at the first stage, that is, decreased sensitivity of cold receptors and increased sensitivity of warm receptors. This is resulted from decrease of pyrogenic substances in the organism. Heat loss is increased.

So, three main stages (periods)are distinguished in the course of the fever which are characterized by a certain disturbance in the interrelation between heat production and heat loss and disorders of the different forms of metabolism, excretion of urine, etc.

**I** - the stage of elevation of the body temperature(stadium incrementi)-heat production is increased, heat loss is decreased;

**II -** the stage of standing of the body temperature at its acme (stadium fastigii)-the ratio of heat production to heat loss is established on a higher level;

**III** - the stage of decrease of the body temperature (stadium decrementi)-heat loss is increased and predominates over heat production(which may relatively even increase.

The main properties of these stages depend on the etiologic agent causing the feverish reaction, development rate of pathological process and organism’s reactivity.

The body temperature may increase rapidly and reach its acme in 2-3 hours (in malaria, croupous pneumonia, scarlet fever, grippe, etc.) or rise gradually during a longer time (in abdominal typhoid, measles, etc.)

The disparity between heat production and heat loss( especially in cases of rapidly rising temperature) is accompanied by chills - a sensation of cold and shivering ,cessation of sweating, pallor of the skin and appearance of ‘’ goose flesh’’. Increase in muscle tone and contraction of various groups of muscles lead to still greater heat production.

The chills are due to stimulation of the nerve endings in the skin as a result of the drop in its temperature caused by spasm of the superficial vessels. Cooling of the superficial layer of the skin reflexly causes shivering. Heat production increases also in the liver and kidneys. Usually blood sugar is slightly increased. Sometimes vomiting, headache, muscle pain are observed. Diuresis is increased.

When the body temperature is already increased, the peripheral vessels dilate, the skin (especially the face) reddens, becomes warm and dry. Sometimes sweating is increased and diuresis is decreased.

At the stage of standing of the body temperature at its acme the dynamic equilibrium is established between heat production and heat loss once again, but on the higher level.

The temperature drops either rapidly, during several hours (crisis) or slowly, gradually, during several days (lysis).The critical drop in temperature, especially in cases of cardiovascular insufficiency, is dangerous because it requires a rapid adjustment of the organism to the new conditions of the internal environment. This may result in shock reaction (collapse).

Heat loss increases as a result of excessive perspiration (very profuse during the rapid drop of temperature)and considerable dilatation of the peripheral vessels. At this stage the temperature is often unstable.

According to the extend of elevation of the body temperature the following forms of fever are distinguished:

1) subfebrile-not above 38o C;

2) moderate-38-39 o C;

3) high- 39-41 o C;

4) excessively high (hyperpyretic)-41 o C and higher.

The body temperature very rarly rises above 41 o C.

The normal body temperature in the human armpit is 36.5-36.8 o C. The difference between morning and evening temperature is no more than 0.6 o C.

In the clinical conditions the temperature of patients is measured at 7-8 o’clock in the morning and at 5-7 o’clock in the evening. Some diseases differ from one another by the characteristic temperature curves. This is connected with the developmental period of the pathogenic agent in the organism. According to the character of the temperature curves the following main forms of fever are distinguished:

1. Continuous fever (febris continua)-the elevated temperature for some time persists on a high level, the difference between the morning and evening temperature not exceeding 1 o C (typhoid fever early in the course of the disease, the fever in croupous pneumonia, typhus and certain other infectious diseases).

2. Intermittent fever (febris intermittens)-is characterized by regular alternation of brief attacks of fever (paroxysms) with feverless periods (apyrexia).High temperature persisrs for several hours, drops to normal and then rises again. This form of temperature curve is characteristic of malaria. Attacks of fever may occur every day (febris quotidiana) every second day (febris tertiana) or every third day (febris quartana).

3. Recurrent fever (febris recurrens)-is characterized by longer periods of pyrexia than in intermittent fever (5-8 days). The duration of these periods corresponds to that of the periods of normal temperature in relapsing fever.

4. Remittent fever (febris remittens)-the difference between the morning and evening temperature exceeds 1 o C. The minimal level of the morning temperature is above 37 o C (during the late course of typhoid fever, sepsis, catarrhal pneumonia).

5. Hectic fever (febris hectica)-the difference between the morning and evening temperature is 2-4o C (in severe cavernous tuberculosis, abscess of internal organs, sepsis).

6. Inversed fever (febris inversa)-the morning temperature is higher than the evening temperature (in sepsis, tuberculosis, brucellosis).

7. Irregular fever (febris irregularis)-the difference between the morning and evening temperature is various in different days (in rheumatism, endocarditis, sepsis, tuberculosis).

8. Undulating fever (febris undulans)-is characterized by the periodic increase and decrease of the temperature (in brucellosis, lymphogranulomatosis).

9. Ephemeral (one-day) fever (febris ephemera) lasts during a short time (several hours). May be caused by mild cases of infectious diseases, sunstroke, blood transfusion, intravenous injection.

10. Atypical fever (febris athypica)-is characterized by irregular fluctuations of the temperature (in sepsis).

There are fevers which at first run the course of febris continua and then change to febris remittens (in typhoid fever).

The type of temperature curve is determined not only by the character of the infection, but also by the reactivity of the organism, the extent of its sensibilization, especially to foreign proteins.

Metabolic disturbances in the fever are caused by various factors:

1) etiological peculiarities, most frequently of the infectious agent;

2) elevation of body temperature;

3) starvation which in some degree accompanies fever since, owing to loss of appetite and digestive disturbances, the organism consumes and assimilates less food than usual.

Metabolic disturbances vary in different fevers, but are nevertheless subject to certain regularities characteristic of most fevers. In most cases metabolism is increased, this increase underlying the greater heat production. The oxidative processes are somewhat intensified partly because of increased respiration and cardiac action. But there may be discrepancy between the amount of oxygen consumed by the organism and heat production, with accumulation of underoxidized metabolites and , in connection with it, decrease in the respiratory quotient.

In fever carbohydrate metabolism is increased which leads to decrease in glycogen in the liver and the possible development of hyporglycemia. These changes are connected with activation of the sympathetic nervous system (increase of synthesis of adrenalin).

The fat metabolism is appreciably increased mainly in lingering fevers of infectious origin. The increased expenditure of fats is due not only to the fever, but also to the concurrent starvation and ,in a certain degree, to intoxication. Ketonemia and ketonuria are sometimes observed as a result of carbohydrate deficiency and decreased oxidation of fats.

In fever involving a high temperature the expenditure of protein is increased out of proportion to that of fats and carbohydrates; elimination of nitrogen in the urine is increased. In cases of moderate fever (in influenza, certain forms of tonsillitis) the share of protein in the total energy balance is often normal( 10- 15%), whereas in fevers with a high temperature the share of protein may reach 30%(in these cases the amount of urea in the urine increases. Disintegration of protein is particularly great in infectious fevers (toxigenic protein disintegration).

Loss of valuable proteins by the feverish organism may be in some degree compensated by consumption of carbohydrates, fats and proteins. Increased specific dynamic effect of protein in severe fevers also explains the increased loss of nitrogen with the urine in high fever.

Degenerative inflammatory changes in tissues, starvation connected with loss of appetite, disturbances in the assimilation of food in infectious diseases lead to rapid disintegration of tissue proteins and negative nitrogen balance.

In fever the water and salt metabolism is more or less altered As a result of increased metabolism and accumulation of underoxidized products at the fist stage of fever the tissues retain water, diuresis is increased. The second stage is accompanied by decreased excretion of urine (hypersecretion of aldosterone). The retention of water is noticeable already at the height of pyrexia. But during the third stage increased excretion of water by the kidneys is observed in addition to the sharp increase of heat loss and excessive perspiration.

The disturbed water metabolism involves retention of chlorides; during the third period, when the excretion of urine begins to increase, more chlorides are eliminated. More phosphates and potassium salts are excreted as a result of tissue disintergration.

The diseases that are accompanied by fever frequently cause severe disturbances in the activity of organs and systems. Most of these changes are connected with the main disease.

Disturbances underlying the disorders of thermoregulation arise in the nervous system. Besides, phenomena due to changes in the body temperature and intoxication occur. Hyperthermia may itself (in aseptic fevers) depending on its intensity, stimulate, and subsequently inhibit the central nervous system. Infectious fevers are often accompanied by sensation of heaviness in the head, general indisposition, clouded consciousness, delirium, hallucinations, etc. Children react to pyrexia by greater excitement than adults do. In emaciated patients fever is attendend with phenomena of depression of the nervous system.

In the vegetative nervous system the functions of its sympathetic division predominate.

As a result of excitation of the sympathetic nervous system the cardiac rhythm is accelerated. Cardiac activity is stimulated by the etiologic factors causing fever (mainly infectious agents and toxins), as well as toxic metabolites. Usually 1 o C rise in temperature is accompained by an increase of 8-10 beats in the heart rate (acceleration of the pulse). But in abdominal fever the pulse rate is decreased (stimulation of the center of the vagus nerve).In inflammation of the meninges (tuberculous meningitis in particular) the pulse rate clearly lags behind the rise in temperature.

The changes in the state of the vessels are connected with disturbances in physical heat regulation. For instance, chills are accompanied by spasm of the peripheral vessels and rush of blood to the internal organs. During the second and especially the third stages of fever the vessels are dilated.

In the beginning of fever the blood pressure is somewhat elevated(increased action of the heart and excitation of the vasomotor centers);but during the last stage the blood pressure drops (weakened heart activity and dilatation of the vessels).The drop in blood pressure may lead to shock or collapse.

Simultaneously with the increased pulse rate and rise in the body temperature respiration is accelerated. Because fever also involves rise in the temperature of the blood and acidosis (as a result of accumulation of acid metabolites). Respiration participates in the physical regulation of heat along with the vascular system and the sweat glands.

Secretion of digestive juices and bile is decreased, the mucous membranes of the mouth and tongue are dry, intestinal peristalsis is disturbed. Some cases are accompanied by constipation with increased putrefaction, accumulation of gases and development of meteorism. Digestive insufficiency and diminished absorption lead to lack of appetite, decreased assimulation of nutritive substances and intoxication.

Function of the kidneys is also altered. Renal filtration is particularly affected by toxins in infectious fevers (scarlet fever, septic diseases).Protein, peptones and albumoses sometimes appear in the urine. In the character and severity of renal affection an important part is played not so much by hyperthermia, as by the infection and intoxication which have initiated the febrile process.

Pituitary body- adrenal system is activated during the fever and the changes characteristic of general adaptation syndrome of Selye take place. Usually fever causes increase of adrenalin’s synthesis in the organism. Pyrogenic substances stimulate also activity of the thyroid gland.

At the first stage of the fever tension of the skeletal muscles is increased. This causes increase of heat production. The more difference between the temperature of the skin and blood –the stronger the muscular shivering.

The body temperature is closely connected with the activity of the cerebral cortex and subcortical centers.

The main center of thermoregulation is hypothalamus. In the animal after complete damage to hypothalamus or dissection of the brain stem under the hypothalamus the organism loses the ability to maintain the body temperature on the constant level and to produce fever. Damage to spinal cord also leads to the disturbance of the thermoregulation. The pyrogenic substances may influence thermoregulation centers also by reflex way.

Numerous facts demonstrate the role of the cerebral cortex in the origen of fever. It is possible to cause fever in dogs by the conditioned reflex way. The temperature of the human organism may increase under the influence of hypnosis, psychical diseases, hysteria.

Endocrine glands also play a part in the development of the feverish reaction. Some analogs of female hormone accelerate formation of the endogenous pyrogenic substances in the leukocytes. Functional disorders in the activity of other glands may influence the process of development of the fever by the way of changing the rate of metabolism, organism’s reactivity, activity of the vegetative nervous system , centers of the thermoregulation . In thyrotoxicosis the feverish reaction develops rapidly and the inflammatory processes are accompanied by higher body temperature, whereas in myxedema and hypofunction of the anterior lobe of the hypophysis comparatively weak course of the fever is observed. Cortisone delays development of the fever (delay of the development of inflammatory processes and formation of leukocytic pyrogen)

Fever is one of the main forms of organism’s defensive reactions which is formed in the process of evolution. If the body temperature is decreased artificially the disorders caused by the feverish diseases in the organism are not eliminated and the outcome of infectious diseases may be more severe. Some infectious diseases (croupous pneumonia, influenza, typhus, etc.) run a graver course in the absence of fever or in cases of weak manifestations of fever.

Certain adaptive reactions, such as phagocytosis, production of immune bodies, and physiological functions, such as hematopoiesis, activity of the enzymes, barrier and antitoxic functions of the liver become more intense at a high temperature.

Increased body temperature causes acceleration of the metabolic processes in the cells and tissues, increase of blood supply of the internal organs and their activation. The number of leukocytes in the blood is increased and phagocytic cells are activated. Besides, antibodies and some nonspecific resistance factors are formed more rapidly. In 38-39.5 o C interferon is synthesized by the greatest rate.

The leukocytic pyrogens consist of 2 protein fractions. One of them exercises pyrogenic influence, whereas the other fraction has antitoxic and antivirus effects. Some microbes (pneumococci,spirochaeta) and viruses (grippe, polyomyelitis) perish in the high temperature.

Rise of body temperature prevents reproduction of some pathogenic agents. For instance, the reproduction rate of the viruses of polyomyelitis is 250 times less in 40 o C than in 37 o C. Some microorganisms, though may reproduce in 40 o C, but their resistance against the antibacterial preparations is decreased, and treatment of disease becomes easier.

To produce fever for therapeutic purposes, especially in certain chronic infections, pyrogenic therapy is applied in the form of inoculation of malaria (in neurosyphilis ), administration of purified pyrogenic substances (pyrexial, pyrogenal) or inductopyrexia, that is, production of fever by electromagnetic induction. Purified pyrogenic substances are applied in the treatment of furunculosis, polyarthritis, eczema. Pyrogens are used in the treatment of the traumatic damages to the nervous system and burns (they delay formation of the hard scars in the nerve fibers and skin).

In inflammatory diseases antipyretic preparations must be applied only in the cases when the body temperature becomes exceedingly high. Because action mechanism of these preparations (especially acetylsalicylic acid) is connected with decrease of synthesis of prostaglandins E. But in these cases synthesis of leukotrienes is accelerated and the conditions are formed for development of allergic diseases. Besides, decreasing of the fever in the initial stage of a number of diseases (especially diseases of the respiratory system) may lead to the long duration of the pathological process and transition to the chronic state.