9.2 Fever

9.2.1 Regulation and control of body temperature

In a healthy individual, body temperature is kept constant in a very small range despite of big differences in temperature of the surroundings and also those in physical activity. Very perfect regulation of body temperature, necessary for optimal progress of enzymatic reactions, is developed in all homoiotermic animals. It doesn't apply to poikilothermic animals. During the most variable changes in human organism, the body temperature may increase. **Fever is a natural reaction during a number of illnesses**. In several cases, absence of the natural reaction is more alarming sign than the presence of fever itself. Fever is usually accompanied by different general symptoms, such as sweating, chills, sensation of cold, and other subjective sensations. Missing of these symptoms during high temperature may be a sign of a serious illness.

The main task in **heat production** has thermogenesis caused by the effect of thyroid hormones. Hormones of thyroid gland stimulate $Na^+ - K^+$ATP-ase found in cytoplasmic membranes. Increased production of heat is achieved by increasing the metabolic processes in which energy is released in the form of heat. The greatest importance is splitting of ATP when 54 kJ are released from one mol of ATP. Skeletal muscles, liver, splanchnic organs, and brain are the biggest producers of heat in an organism. In the heat production the muscles have especially important role. Because of their weight, they are able to produce very large amount of heat very quickly. Increased production of heat takes place in skeletal muscles during increased physical activity. During the digestion, an increased production of heat occurs also in the GIT. Constant body temperature is achieved by perfect nervous regulation. Nervous system maintains the optimal intensity of metabolism and at the same time regulates the amount of heat loss. In early postnatal development, the thermoregulation is inadequate because of immature CNS. Fever is always achieved by reset the center of thermoregulation to higher values. Hyperthermia means overheating of an organism caused only by exogenic causes (e.g. hot environment, hot bath). In this case the center of thermoregulation doesn't change its setting up.

Heat is lost from an organism in several ways. The biggest loss is by conduction. It depends on the gradient between the body temperature and the temperature of the surrounding environment. The second way is **by radiation**. The third way is **by evaporation**. It is used especially during increased production of heat. Distribution of heat is done by blood circulation. Heat goes from each cell to the surrounding liquid and afterwards to the circulated blood. Modulating factor of heat loss is the amount of blood that circulates through the body surface. The big flow through the subcutaneous area and the skin secures the income of heat that may be given to the environment through the body surface. Sweating helps delivering the heat. Sweat glands are controlled by cholinergic impulses through the sympathetic fibers. During intensive sweating, up to one liter of sweat may be formed. When the humidity of the environment is higher, a loss of heat by sweating is easier. When it is necessary to accumulate the heat in an organism, adrenergic stimuli cause reduction of the blood flow through the skin. The skin becomes an isolator decreasing the heat loss to minimum. Control mechanisms regulate the production of heat and its loss. **Production and handover (loss) of heat** are controlled from the center in the hypothalamus. It works on the principle of negative feedback control and includes:

1. Receptors registrating central temperature
2. Effector mechanisms composed of vasomotors, metabolic effectors, and controls of sweat glands
3. Structures recording whether the actual temperature is not too high or too low

Increased central temperature activates mechanisms enabling the heat loss. Low central temperature activates mechanisms enabling the accumulation of heat. These mechanisms work as the thermostat.

In healthy individuals, the body temperature (oral temperature) is somewhere between 36,5°C and 37,5°C. It slightly increases during the day since the morning (from 6:00 a.m.). The peak is reached

at 6:00 to 10:00 p.m. The lowest temperature is between 2:00 and 4:00 a.m. **Diurnal variation** depends on the activity throughout the day. Diurnal variations don't change in persons that work at night and sleep during the day. Such a diurnal variation is also kept when fever occurs. Fever reaches the peak in the evening, and in the morning even a very sick patient may have almost normal temperature. Body temperature changes are more intensive in young person than in old people. The temperature may slightly or temporarily increase in hot environment. Physical activity may also increase the body temperature. In extreme effort, the increase may be very high. The temperature in marathon runners may increase to 39°C to 41°C. The temperature may increase slightly if vasodilatation, hyperventilation, and other compensation mechanisms fail. Small increase in temperature may occur if the surrounding temperature is lower or the jogging is done early in the morning.

Organism uses simple **mechanism for temperature regulation**. It is the blood flow through the skin and subcutaneous area. Vasoconstriction allows the increased accumulation of heat, and vasodilation secures its quick loss. Changes in temperature up to 3°C don't cause an interuption of physiological functions. Spasms may occur during high fever in children. If the body temperature is increased over 42,2°C, irreversible changes in the brain occur. In humans the temperature usually doesn't overcome 41,1°C. Uncontrolled decrease in temperature below 32,8°C is accompanied by confusions and gradual loss of consciousness. If the decrease continues under 30°C, the fibrilation of ventricles occur that is the sign of fatal termination of this condition.

Brown fat that differs from the white one in structure and sites of location has an important function in thermogenesis in newborns and children. It is found between scapulas, on the neck, in axils, around the aorta and the kidneys. It is highly vascularized, and it has large mitochondria in its cells. One could say that while the white fat acts as feather-bed, the brown one is an electrical pillow. Receptors of cold conduct the information to the center of thermoregulation. From this center the impulses run in the sympathetic nerve fibers and lead to the release of norepinephrine in the brown fat. Norepinephrine activates the enzyme lipase. Activated lipase splits the fat to glycerol and free fatty acids (FFA) and the heat is released. Glycerol and FFA remain in the cell and can perform the resynthesis after some time. An adult person has little brown fat.

9.2.2 Pathogenesis of fever

If the body temperature is above 37,2°C and is associated with sweating, hyperventilation, and vasodilatation in the skin, we speak of fever. At the beginning, gradual increase in body temperature is observed together with muscle shivering, vasocontriction in the skin, and piloerection. This situation is called chills. Increased body temperature is achieved by lowered loss of heat. Vasoconstriction in the skin and subcutaneous tissue is the cause of pale color and dryness, the affected person has a feeling of coldness. At the same time the production of heat in the organism increases. The muscle tonus increases, the spasms accur. Spasms may occur mainly in children. When the vasodilatation starts in the skin, the feeling of warmth and sweating occurs.

Fever may be provoked by many stimuli. Most often, they are bacteria and their endotoxins, viruses, yeasts, spirochets, protozoa, immune reactions, several hormones, medications, and synthetic polynucleotides. These substances are commonly called **exogenic pyrogens**. Cells stimulated by exogenic pyrogens form and produce cytokines called **endogenic pyrogens**. Endogenic pyrogens centrally affect the thermosensitive neurons in the preoptic area of the hypothalamus increase the production of heat and decrease in heat loss. The body temperature increses until it reaches the set point. This information is transferred by temperature of blood that flows around the hypothalamus. The decrease of temperature is controlled by activation of mechanisms regulating increased outcome of heat to the surrounding area. Increased outcome continues in favourable case until the new equilibrium is achieved.

The most important endogenic pyrogens are IL-1, IL-6 and cachectin also called the tumour necrosis factor-α (TNF-α). These are glycoproteins that also have other important effects. They are produced especially by monocytes and macrophages but also by endothelial cells and astrocytes. Also the interferons α, β and γ display the pyrogenic activity.

After administration an endotoxin in an experiment, the level of plasmatic TNF-α increases and fever occurs. Increased concentrations of IL-1 and TNF-α are also found in sepsis. The production of

these cytokines is regulated by the positive feedback mechanism. Besides this, macrophages activated by IFN-γ may increase the production of IL-1 and TNF-α primary induced by other stimuli. On the other hand, glucocorticoids and prostaglandins of group E may display inhibitory effect on the production of IL-1 and TNF-α. Released IL-1 and TNF-α are transported by blood. They affect the target cells in the close proximity or in distant sites. The target cells have specific receptors for IL-1 and TNF-α. In the hypothalamus, IL-1 and TNF-α trigger the synthesis of prostaglandis of group E from the arachidonic acid of cytoplasmic membranes of target cells. Precise mechanism by which prostaglandin PGE_2 **reset the central thermostat**, is not known. Aspirin and the non-steroidal antiphlogistics display antipyretic activity by inhibiting the cyclo-oxygenase, an enzyme responsible for the synthesis of PGE_2 (these antipyretics don't inhibit the production of TNF-α or IL-1). Glucocorticoids work antipyretically by inhibiting the production of IL-1 and TNF-α, and by inhibiting the metabolic processes of arachidonic acid.

In the process of fever, IL-1 and TNF-α play the central role. Except introduced activity in fever, **they interfere with many mechanisms in an organism**. Some of their effects are executed with the participation of metabolites of arachidonic acid. IL-1 and TNF-α affect myelopoesis, release of neutrophils and enhancement of their functions. They cause vasodilatation and the increase the adhesivity of cells, increase the production of PAF and thrombomodulin by endothelial cells, proteolysis and glycogenolysis in muscles, mobilisation of lipids from adipocytes, proteosynthesis and glycogenolysis in the liver, induce proliferation of fibroblasts, activate osteoclasts and the release of collagenase from chondrocytes, induce slow wave sleeping activity in the brain, the release of ACTH, beta endorfins, growth hormone and vasopressin, the release of insulin, cortisol, and catecholamines. TNF-α and partially also IL-1 in longlasting operation may cause cachexia mainly by decreasing the appetite. It is so in chronic infections, inflammatory processes, and in neoplastic processes.

Beside that, TNFα and IL-1 significantly increase the immune response by activation of T-cells and stimulation of IL-2 production. IL-1 enhances B-cells proliferation. It is interesting that these processes have the temperature optimum at 39,5°C. It follows that the fever can be supposed as a positive factor. Fever and specific effects of IL-1 and TNF-α form together highly integrated processes that are involved in the response to infection and acute inflammation processes.

Interferons, and especially IFN-γ (formed by T lymphocytes and NK cells) may enhance this reponse. Several parts of this complex response have protective and the others may have malignant consequences. Septicemia, or septic shock is an overshot response of the organism. In this complicated reaction of the organism, it is not easy to decide whether fever should be treated by antipyretics or not. By antipyretics the symptoms of fever may be suppressed but it is uncertain if it is reasonable to suppress also the positive efects of fever and everything that is connected with it. This complex process (fever) mobilizes not only the immune system but also those processes that improve the nutrition of cells and have protective importance on their activity.

In the majority of diseases, fever is caused by pyrogens. There are situations, when fever may be caused directly by changes in the center of thermoregulation without the participation of exogenic and may be also endogenic pyrogens. This occurs in brain tumours, intracranial bleeding, and thrombosis.

9.2.3 Causes of fever

Such a change is considered to be a cause of fever that initiates the production of endogenic pyrogens. Generally, these changes may be divided into several groups:

1. infections caused by bacteria, ricketsia, chlamydia, viruses, and parasites
2. immune reactions, including the defects in collagen, immunological abnormalities and acquired immunodeficiency
3. destruction of tissues, such as trauma, local necrosis (infarction), and inflammatory reaction in tissues and vessels (flebitis, arteritis), pulmonary infarction, cerebral and myocardial infarction, and rhabdomyolysis
4. specific inflammations (sarcoidosis, granulomatous hepatitis)
5. inflammation of intestine and intraabdominal inflammatory processes

6. neoplastic processes with the participation of lymphoendothelial system and hemopoetic system, solid tumours (Grawitz tumour of the kidney, carcinoma of the pancreas, pulmonary and skeletal tumours, hepatoma) Fever is present in complications of solid tumours, usually in metastases that are associated with necrosis of the tumour, obstruction of ducts, or with infection

7. acute metabolic failures such as arthritis urica, porfyria, Addison's crisis, thyreotoxic crisis, and feochromocytoma

8. administration of some drugs

9. dehydration or admistration of salts. That's why fever occurs together with diarrhea.

10. administration of foreign proteins (e.g. globulinum antitetanicum-antitoxic fraction of horse serum) may be the reason of fever's origin.

9.2.4 Progress of the fever and accompanying symptoms

Typical fever runs in certain stages that may be called phases. As **first phase** is entitled **prodromal phase or pre-report phase** that occurs for about 15 to 90 minutes. In this stage, the release of endogenic pyrogen occurs on the basis of exogenic pyrogen's effect. Endogenic pyrogen mediated through PGE_2 affects the thermosensitive neurons of thermoregulatory center in hypothalamus. In this stage, the resetting of thermoregulatory center for a different temperature take place.

The second stage is called the **phase of increase (stadium incrementi)**. It is thought that in this stage the thermoregulatory center is reset. The thermoregulatory center has probably two compartments. The impulses from the sympathetic compartment that are sent by sympathetic fibers to the whole organism are operating in this stage. In cutaneous and subcutaneous vessels, they cause vasoconstriction, thus they decrease the the heat outcome. On the other hand, muscles, liver, and heart, under the influence of sympathetic compartment, increase production of heat that forms, together with decreased outcome of heat, the optimal situation for heat accumulation in an organism. Body temperature increases, but the sick person has a feeling of cold. Thermogenesis participates in this process through thyroxin and triiodine thyronine. In consequence of thyroxin thermogenesis and the activation of sympathicus, the effect of cardiovascular and respiratory systems increases together the basal metabolism. These changes may be measured by increased utilization of oxygen in the organism.

The third stage is called the **climax phase (stadium acme)**. Climax means that the body temperature culminates. At culmination of fever, such a temperature is achieved to which the thermoregulatory center is reset. The center is washed by blood that has the temperature originally adjusted. Because of this, the activation of sympathetic compartments stops. However, the parasympathetic compartment of the thermoregulatory center is activated. Subsequently, the impulses cause vasodilatation of skin vessels and the decrease in peripheral vascular resistance. These changes are the reason of decreased blood pressure and increased pressure in the pulmonary artery. The pressure in the pulmonary artery increases because of vasoconstriction of pulmonary arteriols. The patient has warm and red skin, he sweats, and looses heat by conduction, radiation, and evaporation.

The fourth stage is called the **descent stage (stadium decrementi)**. This stage starts from the peak of fever and is characterized by the decrease of the body temperature. The decrease of fever may be lytical or critical. Critical decrease means the situation when the fever decreases to normal temperature in 1 or 2 hours. With the decrease of fever, also the frequency of puls and respiration is decreased. Sudden descrease especially of longlasting fever may cause temperature crisis. Expressive decrease of fever, decreased puls, and decrease in peripheral vascular resistance may cause the failure of circulation. This is especially dangerous for persons with cardiovascular disease and for old persons.

Some diseases are characterized by certain stereotypic consequence of temperature changes. According to the temperature curve, we may distinguish several types of fever.

1. febris continua is fever in which the temperature changes are less than 1°C in 24 hours

2. febris septica-hectica is fever in which the swings are 3 to 5°C

3. febris remittens is fever with big temperature swings

4. febris intermittens is fever characterized by several hours lasting apyretic periods

5. febris recurrens is fever that reccurs after several days

6. febris undulans is fever in which the halwave lasts several days

7. fever inversa means that fever is higher in the morning than in the evening. This is typical for patients suffering from tuberculosis.

In fever, important changes occur in the function of organism. As a direct consequence, tachycardia is observed. Increased frequency in heart beats by 10 to 15 beats means the increased in the body temperature by 1°C. Except tachycardia, extrasystols may also occur during fever. These may have toxic or infectious origin or may be the sign of myocardial degeneration at longlasting fever. The blood pressure increases in the period of inceasing fever . In the period of decreasing fever, the blood pressure decreases because of the decrease of peripheral vascular resistance and the simultaneously present bradycardia.

Oligemia, caused by evaporation and sweating, may participate in worsening of cardiovasculr functions. In intial stages of fever, up to its culmination, the frequency of breathing increases. During the fever, or after its finish, pathological components-proteins, hyaline casts, and creatinine are present in the urine. Probably, this is caused by the direct damage to the kidneys by the fever itself. Experimentally it was observed that warm water bath of 40°C lasting for several hours doesn'cause similar changes in urine and general condition as fever. Fever has unfavourable influence on the function of the digestive tract. The defect in secretion of digestive juices is observed. This is associated with motor disorder and the disorder of absorption. Such changed functions of GIT may cause the constipation with catastrophical effects especially in old people. Hypoptialism is the part of decreased secretory function of the gastrointestinal tract. At hypoptialism, inflammation of buccal mucosa and the tongue is present as well. In general, the patient loses appetite what is caused by direct activity of TNF-α but also by functional changes in the digestive tract.

Oxidative processes speed up during the fever what may be demonstrated by the incresed utilization of oxygen. During the fever or after its finish, hyperglycemia may be ascertained. In general, the catabolism of proteins with negative nitrogen balance increases leadeing to the losses of protein that may reach 300 to 400 grams per day. Decreased diuresis associated with increased protein catabolism often leads to the rise in metabolic acidosis. These metabolic changes may be improved in the phase of polyuria that starts after the decrease of fever.

When the body temperature increases by 6°C a situation not compatible with life is formed. Subjective feeling of fever is highly variable. Some persons percieve already a small increase in body temperature, others don't feel even the increase of temperature to high values. This occurs in persons with longlasting increase of body temperature. A patient with tuberculosis sometimes doesn't even feel the temperature of 39°C. In most cases, the fever is associated with subjective dyscomfort such as uncertain headache, arthralgia, pain in muscles and in the back. The cause of these symptoms is not completely clear.

Chills may accompany any fever. It is typical for pyogenic infections associated with bacteremia. It may also occur in noninfectious diseases such as vasculitis or lymphoma. Chills may be provoked by antipyretics that cause sudden decrease of body temperature. This effects of antipyretics is seen especially if they are given in the phase of increasing temperature.

Sweating. Diffuse sweating usually occurs in culmination of fever. It may be very unpleasant for some persons. However, it is the natural reaction at the process of fever.

Changes in mental condition are present in very young and very old persons. They may be very mild or may develop into delirant state. Expressive changes in mental condition may be sometimes observed in alcohol drinkers, cardiovascular patients, and senile persons. TNF-α and IL-1 cause the release of β-endorfins in the brain that may participate on changed mental condition.

Spasms are present in children to 5 years of age. Most often they develop in the phase of increasing body temperature.

Herpes labialis. Increased body temperature may activate latent virus of herpes simplex. From unclear

reasons, it often occurs in pyogenic bacterial infections (pneumococcal, streptococcal, meningococcal), in malaria, and in ricketsioses. Herpes labialis to some extent a sign of suppressed cellular immunity.

Utility of fever. Fever slightly increases immune reactions, increases chemotactic, phagocytic, and bactericidal activity of polymorphonuclear leucocytes. Up to certain value, it stimulates the processes of antibody production.

Concomitantly, it slows down the proliferation of microorganisms. Increased body temperature causes a decrease in the amount of plasmatic iron, zink, and copper. This decrease is not favourable for the growth of microbes. High temperature causes destruction of lysosomes and the whole cells. This is a way by which the body defendes itself against microbes but also against reglication of viruses. The increased production of interferons also acts against viruses.

In general, fever is considered to be a pathological reaction. However, it belongs to compensatory mechanisms and has important roles in defence processes. Therefore, medication of actual fever can't be the target of treatment. Infectious disease without fever means a prognostically bad medical finding.

Harmfull effects of fever. They may come into consideration at high temperatures, if fever lasts too long, and especially if the patients are suffering from an additional disease, too. Increased basal metabolsim, minute heart volume, and water and salt loses may complicate other basic illnesses. Very high temperature suppress immune mechanisms. Longlasting fever causes dysfunctions of parenchymal organs. It is so in malignant (extreme) fever, febrile spasms, epilepsy, cardiac problems, and the disease of the central nervous system. Fast decrease of fever may endanger the patient by fast lowering of the blood pressure.

9.2.5 Fever from the clinical point of view

Fever may have certain signs in relation to its course. It has diagnostic importance and certain information value. Is several disease, however, it doesn't necessarily have certain characteristics.

Fever in infectious diseases usually is of short duration. Generally, it is limited to 2 week period. During infectious diseases fever has the following characteristcs: sudden start of fever, temperature over 38,5°C, fever without chills, symptoms of respiratory infection, muscle and joint ache, headache, nausea, vomitting, diarrhea, enlarged lymph nodes or spleen, meningeal symptoms, and dysuria.

Similarly to infectious diseases, acute leukemia or vasculitis may manifest in the same way.

Long duration (weeks or months) is always a very serious problem. If it is not possible to determine the cause of fever at the beginning, it is called the **fever of unknown origin (FUO)**. This term is used to describe fever lasting at least 2 weeks, reaching temperatures above 38,2°C, and the cause of the origin is uncertain.

Fever may last long **in some infections** with subacute or chronic course. Those may be hired abscess in the abdominal cavity or in the abdominal organs (abscess of the liver, spleen, subfrenic abscess, diverticulitis and an abscess in the small pelvis).

Longlasting fever may also occur **in renal infections** and in intravascular infections (acute infections of the urinary tract, bacterial endocarditis).

Unwanted are the **iatrogenic infections** at catheterisation or at fistula treatment. They cause big troubles and may have untypical course associated with fever.

Deep mycosis and tuberculosis, complications of AIDS, complications of immunosuppressive treatment are accompanied by fever. Viral infections, ricketsioses and chlamydia infections are accompanied by fever and lymphadenopathy.

Neoplastic processes are very serious problem. In some of them, fever of unknown origin may be present for a long time. Sometimes after months or even after year or two, other symptoms of neoplastic disease may be detected. In several cases fever has typical progress (Pel–Ebstein fever at Hodgkin's lymphoma). Acute leukemia may be, at the beginning, considered to be an infectious disease. The temperature reaches up to 40°C. Fever may accompany also the solid tumours. The cause may be the obliteration of glandular ducts or necrosis of the tumour and/or metastatic spread.

Diseases of connective tissue are accompanied by fever. It's present at rheumatic arthritis, periarteritis nodosa, systemic lupus erythematosus, and in polymyalgia rheumatica.

There are many other disorders and changes of organism in which fever develops. Those may be hid-

den hematomas, hemolytic crisis, pulmonary embolisation, and thermoregulatory dysfunction at metabolic and endocrine disorders. Sometimes **psychogenic fever** may occur. It happens in patients with psychopathology or in pharmacofags. In these cases the frequency of heart beats even at high temperatures increase only slightly.

Habitual hyperthermia (37,2–38°C) is detected in children and young women. It is associated with the signs of psychoneurosis, asthenia, complete weakness, and insomnia. They often have different unpleasant subjective feelings that force them to think about their high temperature.

Drug-induced fever is a serious problem. If we take into consideration that the patient with infection is treated by antibiotics that may cause fever, we find out that it's an excessive complex problem. Of medications that cause the fever the antibiotics are most frequent (especially β-lactamase antibiotics and penicilins) but also sulfonamids, nitrofurantoin, antituberculotics, barbiturates and laxatives. Drug-induced fever doesn't have characteristic features. Most often it occurs 5 to 10 days after the start of treatment but it may occur also right after the first dose. Most probably, the drug acts like an exogenic pyrogen.