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Disorders of Thermoregulation. Pathogenesis of Tumor Growth

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PREFACE

The knowledge about typical pathological processes is an essential part of Pathophysiology study. This manual presents information about thermoregulation pathologies and tumor growth pathogenesis.

Thermoregulation disorders are quite common in medical practice. Fever accompanies various diseases, both of infectious and non-infectious origin. The study of the etiology and pathogenesis of this typical pathological process is necessary and important for a doctor of any specialty.

Knowledge of the causes and mechanisms of fever development will allow developing rational approaches to the pathogenetic treatment of fever.

In addition to fever, other disorders of thermal homeostasis are known, such as hyperthermia and hypothermia. Knowledge of the causes and mechanisms of their development will be useful for a correct differential diagnosis and further treatment.

The study of tumor pathogenesis is currently very important. In recent years, the morbidity and mortality of people from malignant tumors continues to increase in most countries of the world. Nowadays, there are about 10 million cancer patients in the world. Therefore, it is extremely important to understand the etiology and pathogenesis of tumors, to know the difference between benign tumors and malignant tumors, to understand the consequences of the presence of a tumor in the human body. Modern methods of diagnostic help to detect the tumors on early stages of their development and to influence its progress by different methods of treatment.

The knowledge of tumor pathogenesis obtained in the course of Pathophysiology will be useful both for senior courses study of Oncology and for future professional activity.

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DISORDERS OF THERMOREGULATION

PHYSIOLOGY OF THERMOREGULATION

The ability to maintain body temperature at a relatively constant level (isothermia) is a vital feature acquired by humans and higher homeothermic animals in the process of evolutionary development, allows to provide full adaptation of the organism to the conditions of the external environment (to meteorological and climatic-geographical factors), which changing conditions. The first animals appeared on the Earth were not able to maintain their body's temperature were poikilothermal (coldblooded). The inability to maintain body temperature at a constant level regardless of fluctuations in external temperature, made animals extremely dependent on climatic factors. As a result, periodically occurring cold snaps led to the extinction of a huge number of poikilothermic animal species, including giant dinosaurs. Some species of poikilothermic animals that occupied narrow ecological niches in the course of evolution, have survived to this day (fish, amphibians, reptiles). The evolutionary transition from poikilothermy to homeothermy required the involvement of complex mechanisms that provided both higher rates of heat production and regulation of heat loss in conditions of significant fluctuations in temperature of surrounding.

Homeothermia is developed in the process of ontogenesis: newborns of all mammalian and human species have an imperfect system of thermoregulation and are much more susceptible than adults to hypothermia and overheating. In old age, the mechanisms of thermoregulation mechanisms become less perfect again, and the temperature factor has a much greater pathogenic effect than for those who are in the middle age – the height of their physical strength. Adult mammals of some species have the ability to lose their homeothermicity periodically (during winter) while undergoing the process of hibernation. During this period, they demonstrate acute decrease of the metabolic processes level of, and they become to some extent poikilothermic.

Despite the fact that the temperature of the internal environment of the homeothermic animals' organism is a fairly rigid physiological constant (in human when measuring the temperature in the rectum it is normally maintained in the 37.2 - 37.5°C), isothermal compartments, in the full sense of the word, are only blood circulating in the deep vessels of the body and internal organs, protected from the environment by powerful muscle and fat layers. The temperature of the outer skin of the body varies within a very wide range.

From the thermoregulation point of view, our organism consists of two parts – homeothermic and poikilothermic. The first part includes the internal organs. The liver has the highest temperature, followed by the blood in the aorta, the organs of the thoracic and abdominal cavities, the brain and spinal cord. These organs, which are located deep in the body and have a constant temperature, are called the core, or nucleus. The organs and tissues located in the periphery, primarily skeletal muscles, have a low temperature and are also easily changed in response to external influences. The notional average temperature measured under the arm is 37^0C.

The human body temperature is characterized by circadian biorhythms with some spikes of highs and lows – in the 0.5° - 0.7° C. The maximum body temperature is at 16-18 hours, the minimum is recorded at 3-4 hours. Daily fluctuations in body temperature reflect the rhythmic change in the intensity of metabolic processes in the body. The animals with an active nocturnal lifestyle, the fluctuations have the opposite direction.

The constancy of the temperature of the internal environment of the body is achieved by balancing the processes of heat production and heat loss. In other words, isotherms are based on physiological mechanisms that jointly regulate these processes. Taking into account their peculiarities, thermoregulation is divided into chemical and physical.

Chemical thermoregulation (heat production) is carried out through exothermic biochemical reactions, i.e. those that generate heat.

There are two main ways of heat generation:

- during the breakdown of ATP (muscle contraction), about 40% of the energy stored in energy stored in it is released as heat – contractive thermogenesis;
- basal rate of metabolism of all cells of the body – heat is being produced both in catabolic and anabolic reactions – non-contractive thermogenesis.

Thus, heat production depends on the intensity of metabolic processes, primarily in the liver, and on muscle work. In the latter case muscle tremors, i.e. the chaotic contraction of skeletal muscle fibers. At the same time, the muscle as a whole, developing tension due to the contraction of its individual elements, does not perform any work, and almost all the energy released during the breakdown of ATP is realized in in the form of heat.

To summarize, the main heat generating organs are muscles and liver.

Heat production can be influenced by:

- Increased rate of metabolism caused by muscle shivering (trembling) ;
- Increased rate of metabolism caused by the effect of thyroxin on the cells;
- Increased rate of metabolism caused by the effects of epinephrine, norepinephrine and sympathetic stimulation on the cells.

Physical thermoregulation (heat loss) is carried out by the loss of heat by heat conduction, heat radiation and evaporation. The processes of heat loss involve the skin, mucous membranes, lung, cardiovascular and urinary systems.

The condition of the skin vessels plays a particularly important role in the heat loss process, as well as heart rate and respiratory rate. Increased heart rate and dilation of the skin vessels leads to the fact that increased amount of blood that passes through superficially located vascular pathways per unit of time, increases heat transfer. A similar result occurs with an increase in respiratory rate because of the removal of warm air.

A powerful factor in heat transfer is the evaporation of liquid (sweating) from the surface of the human body. Evaporation of 1 g of water from the skin surface results in a heat loss of 2.43 kJ (0.58 kcal). During hard physical work in conditions of high ambient temperature, sweating can reach 10-12 liters per day. It is important

that a large number of salts (sodium chloride) and vitamin C is lost with sweat. In this regard, the normal consumption of these substances should be expanded in the diet of people working in hot shops and working in hot workshops and in hot climates.

Nervous mechanisms of thermoregulation are based on reflex arches, which include receptor formations (heat and cold receptors), located mainly in the superficial layers of the skin. In addition, cold receptors (more numerous than heat receptors) are also localized in the internal organs. Heat receptors are most active in the following temperature range temperature range of 40-46 °C, the highest activity of cold receptors is highest at 20-36 °C. The impulse from the receptor apparatus reaches a number of from the receptor apparatus reaches a number of major centers of autonomic regulation – the hypothalamic structures. The efferent part of the reflex arc are sympathetic and parasympathetic nerve fibers that innervate the internal organs and blood vessels. The efferent impulse is also carried out by motor somatic fibers, which regulates the activity of skeletal muscles. It is important to keep in mind that the structures of the central nervous system (hypothalamus system (hypothalamus, reticular formation, spinal cord, etc.) have their own thermoreceptors. In the hypothalamus, they are concentrated in its anterior part - the preoptic zone. Thus, the human body has a double system for controlling body temperature: the influence of the environment (thermal or cold) is carried out by skin receptor formations, and the temperature of the internal environment is precepted by thermoreceptors of internal organs and structures of the central nervous system.

The hypothalamus plays a major role in the mechanism of thermoregulation. It contains the main centers of thermoregulation, which coordinate numerous and complex processes that ensure that body temperature remains constant.

The neurons of anterior hypothalamus control the processes of heat loss (they provide physical thermoregulation – vasoconstriction, vasodilation, sweating). When the neurons of the anterior hypothalamus are destroyed, the organism poorly tolerates high temperatures, but physiological activity in cold conditions is preserved.

The neurons of the posterior hypothalamus control the processes of heat production (they provide chemical thermoregulation – increased heat generation, muscle trembling). If they are damaged, the ability to increase energy exchange is impaired, so the body does not tolerate cold well.

Thermosensitive nerve cells of the preoptic area of the hypothalamus directly "measure" the temperature of arterial blood flowing through the brain, and have a high sensitivity to temperature changes (able to distinguish the difference in blood temperature of 0.011 ° C). The ratio of cold- and heat-sensitive neurons in the hypothalamus is 1:6, so the central thermoreceptors are mainly activated when the temperature of the "core" of the human body rises.

Analyzing the information about the temperature value of blood and peripheral tissues, the average value of body temperature is continuously determined in the preoptic area of the hypothalamus. These data are transmitted through insertion neurons to the group of neurons of the anterior hypothalamus, which set a certain level of body temperature in the organism - the **"setting point" of thermoregulation**. Grounded on the analyses and comparisons of the average body temperature and the target temperature to be regulated, the "set point" mechanisms via effector neurons of the posterior hypothalamus influence the processes of heat loss or heat production to bring the actual and target temperatures in a line.

External temperature information comes from skin thermoreceptors. Internal body temperature is monitored by central thermoreceptive neurons in the anterior hypothalamus that respond to blood temperature. This system works using negative feedback for which the set point (reference point) is normal body temperature. In response to error (mismatch) signals, reactions occur to return the body temperature to the set point.

Thus, due to the autonomous function of the thermoregulation center - hypothalamus, a constant balance between heat production and heat loss is maintained in the human organism, which allows keeping the body temperature within the optimal limits for vital activity of the organism.

The hypothalamus directly influence endocrine system to control thermoregulation through a hormonal mechanism.

Together with the pituitary gland, the hypothalamus forms the hypothalamic-pituitary system, in which the hypothalamus controls the release of pituitary hormones and is the central link between the nervous and endocrine systems.

The hypothalamus controls the processes of heat production and heat loss by sending nerve impulses to the glands of internal secretion, mainly the thyroid gland, and the adrenal glands.

Participation of the thyroid gland in thermoregulation is due to the fact that the effect of low temperature leads to an increased release of its hormones (thyroxine, triiodothyronine), accelerating basal metabolism and, consequently, heat generation.

The role of the adrenal glands is connected with the release of catecholamines (adrenaline, noradrenaline, dopamine) into the blood, which, by increasing or decreasing oxidative processes in tissues (e.g. muscle), increase or decrease heat production and narrow or enlarge skin vessels, changing the level of heat loss.

FEVER PATHOGENESIS

An **increase in body temperature** is a very frequent symptom of many diseases. There are two types of temperature rise – fever and hyperthermia.

Fever was developed and was fixed by natural selection in the evolution of higher warm-blooded animals as a reaction to infectious agents, is an adaptive reaction that increases the natural resistance of the organism, although under certain conditions it can be harmful to the patient.

Fever is a typical pathological process, which is manifested by the body core temperature increase. Fever is typical to human beings and higher homo-thermal animals.

The substances which can cause fever are named pyrogens. There are primary pyrogens (exogenous and endogenous) and secondary pyrogens (endogenous). Primary exogenous pyrogens are also divided into infectious and non-infectious

ones. In the process of evolution, fever has developed primarily as a response to the penetration of microorganisms and their toxins into the body. At the same time, it is known that it can arise from the ingestion of substances unrelated to infection.

Infectious pyrogens include bacteria, viruses, protozoa, fungi. Fever development is determined by thermostable polysaccharides and lipopolysaccharides complexes which are the part of the microbial cell membrane. Pyrogenic properties of lipoid polysaccharides don’t depend on pathogenicity and toxicity of microorganisms. Thus, highly pathogenic microorganisms that cause cholera, tetanus and botulism development usually do not cause fever reaction.

Evolutionarily, fever appeared as a reaction to the invasion of microbes and their toxins into the body, so it is characteristic of infectious pathology. Microorganisms include pyrogenic substances (external, exogenous pyrogens). They are a component of microbial toxins. The endotoxins of Gram-negative bacteria are studied in this regard in total. They consist of three fractions - lipid, polysaccharide and protein. The lipid fraction (lipoid A) has pyrogenic properties. It was possible to isolate highly purified pyrogens from Gram-negative bacteria and create preparations for clinical use - pyrogenal, pyrexal, pyromen.

The active substance in them is lipoid A. Interest in endotoxin sharply increased when it was noted that under its influence in animals and humans, the course of a number of diseases, including tumors, brain syphilis, etc., is facilitated. In this connection bacterial pyrogens began to be used in the clinic. The difficulty, however, was that such pyrogens together with fever caused intoxication phenomena in the form of hemorrhagic shock, thrombosis, skin lesions like Schwartzman's phenomenon, etc. In this connection, such a technology of pyrogen production was worked out so that its positive effect (pyrogenic, therapeutic) was preserved and toxic at the same time was eliminated.

Gram-negative bacteria served as starting material for obtaining pyrogens as medicinal agents. The domestic drug pyrogenal was obtained from Pseudomonas aerugenosa, to induce fever in humans about one μg of pyrogenal per 1 kg of body weight must be administered. Temperature rises 40 90 min after parenteral

administration of pyrogenal and is maintained for 6 hours. Nowadays pyrogens are synthesized; they are used to increase body temperature artificially (pyrotherapy).

In addition, primary pyrogens can be formed during bone fracture, blood transfusion. These substances are formed during damage or destruction of own tissues and have an effect on the organism similar to the action of "real", i.e. microbial pyrogens.

Non-infectious pyrogens of exogenous origin can also cause the development of fever. These substances may have various chemical structures. In most cases, they are proteins, lipids or nuclear acids. Parenteral injections of the sterile protein – or lipid containing substances (whole blood transfusion, blood plasma transfusion, and serum or immunoglobulins injections) cause fever development.

Fever caused by primary endogenous non-infectious pyrogens appears under the influence of many factors, which provoke tissues damage and aseptic inflammation. Noninfectious fevers appear under burns, mechanical traumas, after operations, internal hemorrhages, infarcts, allergic reactions, autoimmune processes and etc.

Other causes of non-unfectious fever include:

- the presence of necrotic tissues in a particular part of the body (heart attack myocardial infarction and other organs);
- foci of aseptic inflammation (pancreatitis, gout, thrombophlebitis, etc;)
- allergic diseases (pollenosis, serum sickness, etc.);
- internal haemorrhages, increased haemolysis of erythrocytes;
- development of malignant tumours;
- aseptic tissue injury (after surgical operations);
- after haemotransfusions, parenteral administration of vaccines, serums and other protein-containing fluids.

The development of fever in these cases is determined by the emigration to the site of inflammation of leukocytes, which become activated and begin to produce leukocyte pyrogens. It has been established that neutrophil granulocytes and macrophagocytes, both mobile and fixed in tissues (pulmonary macrophages, spleen

and lymph node mononuclei, macrophagocytes of peritoneal exudate) participate in the synthesis of leukocytic pyrogens. No pyrogens are formed in lymphocytes. Synthesis of leukocytic pyrogens is encoded in the genome of leukocytes and starts from the moment when primary pyrogens get into macro- and microphagocytes and begin to activate metabolic processes in them, including the synthesis of pyrogens, as well as their release into the internal environment.

The process of leucocyte pyrogen formation can also be induced by other substances, including hormones (increased body temperature in women during the normal menstrual cycle). Fever in allergic (sterile) inflammation is explained by the fact that when leukocytes are attracted in the immune response, there is a depression of genes encoding the production of pyrogenic substances. Antigen-antibody complexes stimulate leukocyte pyrogen production. In infectious diseases, sensitization leads to more severe fever on repeated contact with the causative agent. Primary pyrogens, penetrating into the body, do not cause fever, but only initiate this process by inducing their own cells to produce special protein substances (secondary pyrogens), which in turn affect the mechanisms of thermoregulation and lead to fever.

Secondary pyrogens are cytokines that are produced and released by activated leukocytes (neutrophils, monocytes, and by tissue macrophages). Pyrogenic properties are peculiar to the following cytokines: IL-1, IL-6, TNF and gamma-interpherone. Pyrogenic cytokines are non-specific and they are synthesized in every case of primary pyrogens entrance or development in the organism.

Interleukin-1 is represented by two polypeptides: IL-1α (molecular weight - 33kD) and IL-1β (17.5kD). The latter is predominant in humans. The peptides have homologous 26% of amino acids, have an identical spectrum of biological activity, bind to the same receptor, but are products of two different genes and can be either membrane integral and secretory soluble molecules.

Stimulators of IL-1 release are:

1) Bacterial cell wall components (lipopolysaccharide and muramyldipeptide - a bacterial peptidoglycan) acting on the cellular receptor CD14, which is found on macrophages, Langerhans cells and possibly granulocytes.

2) Inflammatory mediators released by activated cells.

Macrophages produce the most of IL-1. However, other calls are also significant sources of this cytokine: macrophage-like dendritic and glial cells, endothelium, and fibroblasts, B-lymphocytes and some epithelial cells, e.g, keratinocytes. In principle, any nuclear cell in the body is likely to express interleukin-1 genes, any nuclear cells in the body are probably capable of expressing interleukin-1 genes. From the other hand, all body cells have receptors to IL-1. This makes IL-1 the most diverse in terms of of all cytokines involved in the formation of the acute phase response. IL-1 peptides are the most pyrogenic cytokines: when administered intravenously to humans, they cause chills and fever up to 39 °C within 1 hour in doses of 10-30 nanograms/kg of body weight. IL-1 is a slow-wave sleep peptide. Its hypnotic effect causes a decrease in performance and physical inactivity in prodromal syndrome.

Interleukin-6 (IL-6) is synthesized by activated lymphocytes, fibroblasts, endothelial cells, T-lymphocytes and some B-cells. It is the most important actor of the synthesis of "acute phase proteins", i.e. globulins, which plasma concentration increases in any inflammation, infection, immunopathological processes. The target of its action are hepatocytes, thymocytes and lymphocytes. For myeloid semi-stem cells, it serves as a growth factor, promoting the production of all granulocytes and monocytes, platelets and erythrocytes. It is a differentiation peptide for plasma cells that synthesize antibodies, as well as for the malignant clone in myeloma, a stimulator of proliferation of skin keratinocytes and mesangial cells of the kidneys. There is evidence of its role in thermoregulation and induction of fever, but as a regulator of temperature homeostasis itself, IL-6 has the lowest pyrogenic activity when compared to other cytokines. Thus, when administered intravenously to humans, it causes fever up to 39C in a rather high dose - 1 microgram per kg of body weight. Apparently, this signal is mainly intended for the implementation of non-

temperature components of the acute phase response. Synthesis of IL-6 synthesis is stimulated by IL-1 and tumor necrosis factor. IL-6 is much more stable than its inducers, so it is believed that this cytokine is thought to make a crucial contribution to the acute phase response. Even significant doses of IL-6 do not cause cell necrosis or apoptosis and are not lethal, in contrast to the above-described regulators. Apparently, this particular cytokine directs the normergic response of the acute phase.

Tumour necrosis factor (TNF) is known in two fractions cachexin (TNFα), which is produced by macrophages, lymphocytes, adipocytes and mast cells, as well as microglia, and lymphotoxin (TNFβ), a product of T lymphocytes. The former is a monomer, and the latter is a trimer of the same subunit with a molecular weight of about 17 kD. It causes chills and fever up to 39 °C 1 hour after intravenous administration to humans in slightly higher doses than interleukin1: 50-100 ng/kg body weight. In addition to the pyrogenic effect, TNF has many other important effects. Cachexin inhibits the activity of the hunger center and stimulates the satiety centre in the hypothalamus, being a strong anorexigen. Hyperproduction of TNF by mononuclear cells and possibly by glial tumors, is the morphological basis of a peculiar syndrome characterized by complete loss of appetite and profound weight loss. Previously this condition was considered to be psychogenic, so it has a historically established name "neurogenic anorexia". Cachexia in infections, especially chronic ones, as well as in tumors and leukemia, wound exhaustion - associated with production in all these situations by TNF. It is this cytokine that causes anorexia and hypercatabolism during the acute phase response. It is also a strong counter-insulin factor. TNF is an activator of the endothelium and all types of leukocytes (primarily their cytotoxic functions), a stimulator of cellular cell adhesion. It promotes the transition of macrophages into multinucleated giant cells, which synthesize even more TNF. Under the influence of TNF, angiogenesis may be enhanced, it is involved in the launch of acute phase protein synthesis by the liver and enhances the expression of HCV antigens and Fc receptors on a variety of targets. In detailing the immunological functions of TNF, we would like to draw

attention to its ability to induce hepatocyte apoptosis at high doses, gastrointestinal cells, endothelial cells and even neurons apoptosis. TNF and IL-1 are particularly toxic when acting together. They can block membrane digestion and intestinal motility, provoke vomiting and diarrhea, cause destruction of hepatocytes, and provoke hyperkalaemia and acidosis. The combined toxic effect of these cytokines, with their massive release and prolonged in the bloodstream can be fatal. They stimulate the endothelium to produce coagulants, in particular, thromboxane A2 and leukotriene E4 and contribute to the development of DIC syndrome, increase the production of platelet activation factor, nitric oxide and myocardial depressor polypeptide. The latter causes vasoconstriction in the internal organs and and decreases myocardial contractility.

FEVER PATHOGENESIS

Fever usually proceeds in three stages: temperature increase stage, standing stage and decrease stage.

Temperature increase stage – stadium incrementi.

Fever and inflammation are closely related by immune cell that are involved in both typical pathological processes. Pyrogenic cytokines synthesized by activated leukocytes in the process of phagocytosis reach nervous cells of the hypothalamic thermoregulation center. It results in the activation of membranous phospholipase and arachidonic acid release from nervous cell membrane. This leads to increased synthesis of prostaglandin E2 in the cells of anterior hypothalamus. Prostaglandin E2 activates adenylate cyclase and inhibits phosphodiesterase. As a result, accumulation of cAMP takes place in the nervous cells of thermoregulation center. This leads to the changes of metabolism in these neurons and decreases excitation threshold of cold-sensitive neurons.

Because of this effect, the normal blood temperature is perceived as a lower one and adjusting point of thermoregulation center becomes higher than normal. In order to keep the body’s temperature within new limits, heat loss is restricted, and heat production is increased.

The temperature rise stage is characterized by the prevalence of heat generation over heat loss. Increased heat production is due to increased oxidative processes in the body's cells, primarily in the liver, etc. (non-contractive thermogenesis). Muscle tone increases, sometimes turning into tremors (contractive thermogenesis). In newborns and young children, shivering is not observed, but increases significantly non-contractile thermogenesis due to stimulation by catecholamines of oxidative processes in brown fat.

The decrease in heat transfer occurs with the participation of the sympathetic nervous system. Emphasizing its role, it is interesting to note that against the background of α-adrenoceptors, fever does not occur. Impulses from the preoptic area of the of the hypothalamus cause excitation of the centers of the sympathetic nervous system in the posterior hypothalamus. This is accompanied by spasm of superficial vessels and blood outflow into the deep vascular bed. As a result, the following decreases heat loss by convection, heat conduction and heat radiation; in addition, due to a lack of blood supply, the function of the sweat glands is suppressed, and sweating decreases. The skin becomes pale and dry. The extremities are cold. There is irritation of the of skin thermoreceptors, accompanied by additional reflex excitation of "cold" neurons in the preoptic area and centers of the of the sympathetic nervous system in the posterior hypothalamus. This accelerates the increase in body temperature. With a rapid increase in body temperature chills occur, the patient seeks to reduce heat loss by wearing additional clothing and moving to a warm place.

Heat irradiation decreases because of skin peripheral vessels constriction, sweat secretion inhibition and decrease of evaporation. In animals, hair bulb muscles are contracted which dishevel wool, and this increases heat isolation. Human being has an equivalent – a “gooseflesh”. Goose flesh or goose bumps are the bumps on a person's skin at the base of body hairs which involuntarily develop when the person is cold or experiences strong emotions. The reflex of producing goose bumps is known as piloerection, or the pilomotor reflex. Goose flesh is the sign of chill development. Chill pathogenesis may be explained in the following way. Periphery

vessels constriction leads to irritation of skin cold receptors. This leads to increase of sensitive information transmission from skin cold receptors to CNS that results in thermoregulation center excitation. As the response, we observe the appearance of muscular trembling, pilomotor reflex, feeling of cold, pale skin color.

There are several options for changing thermoregulation in the first stage of fever:

1) there is a significantly pronounced increase in heat production and a decrease in heat loss;

2) both heat production and heat loss increase, but the first process prevails over the latter;

3) heat transfer mainly decreases, while heat production heat production increases to a weak degree.

Most often, an increase in body temperature is caused by a decrease in heat loss than an increase in heat production.

The body temperature rises until it reaches the level to which the "set point" has moved to. Maximum rise in body temperature in fever rarely reaches 41.1 °C. It has been established that limiting the excessive severity of body temperature rise in fever is due to the functioning of a special mechanism called endogenous antipyretic response. Arginine vasopressin is involved in this process. The development of fever is accompanied by the release of arginine vasopressin into the cerebrospinal fluid and the ventral septum of the brain. It has been established that IL-φ not only acts as a secondary pyrogen, but also participates in endogenous in endogenous antipyretic activity, promoting the release of arginine vasopressin from the paraventricular nuclei. In addition to arginine vasopressin, other antipyretic agents are involved in ACTH, glucocorticoids, melanocyte-stimulating hormone, and angiotensin are involved in the limitation of fever. The antipyretic effect of steroids is associated with their effect on the production of antiphospholipase proteins that inhibit phospholipase A2, and thus the synthesis and release of prostaglandins - mediators of fever.

The temperature rise in the first stage of fever in some diseases occurs quickly, within a few hours (influenza), while in other cases it takes several days for the temperature to reach the highest level (typhoid fever). This mainly depends on the cause of the fever.

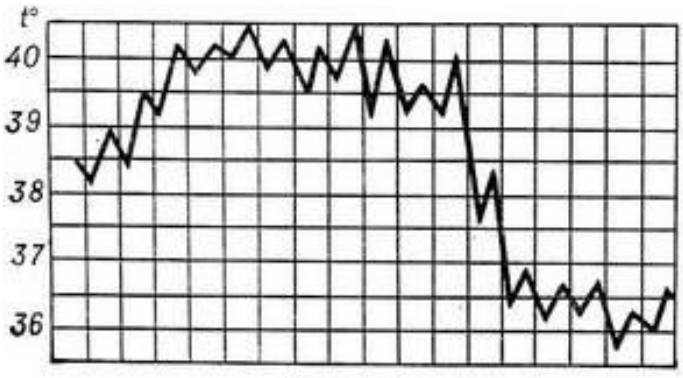
The temperature of surrounding does not have influence on fever development and body temperature. For example, the person with influenza will develop fever both in high temperature (+40 C) and cold (0 C) surrounding. The level of body temperature increase is directly dependent on the amount of secondary pyrogens. In the cases of low leukocytes quantity or functional activity body temperature will not increase significantly despite the high amount of primary pyrogens.

High temperature standing stage – stadium fastigii.

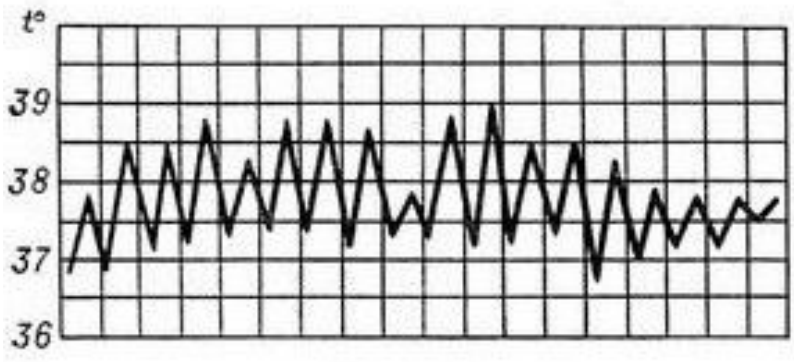
At the first stage of fever temperature reaches some level, where it stands during the second stage. The second stage of fever is characterized with the normal balance between heat production and heat loss. Temperature maintenance at a high level can be explained by heat regulation center adjusting point change under secondary pyrogens influence.

Heat irradiation increases in comparison with the first stage and there is no further temperature increase. Heat irradiation intensification is provided by means of peripheral vessels dilation. Skin paleness is changed to hyperemia, the skin becomes hot by touch. Fever sensation appears. The dynamics of temperature increase in the second fever stage may be different. It may be determined with the features of infectious agent that caused fever reaction and with the peculiarities of the human organism. Some diseases are characterized by certain stereotypic consequence of temperature changes. According to the temperature curve type, we may distinguish several types of fever.

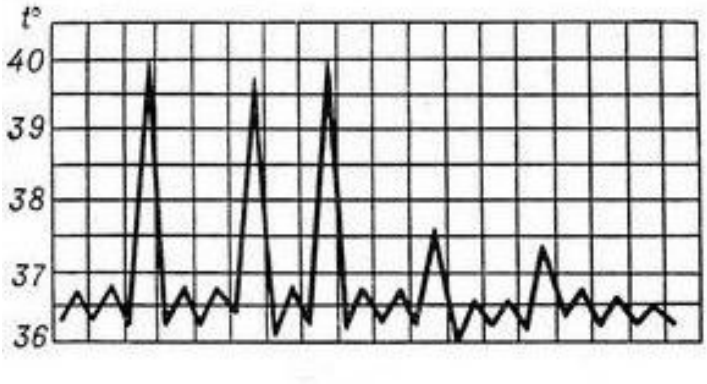
Febris continua is marked by temperature fluctuation within 1^{o} C range during a 24-hour period (abdominal typhus, paratyphoid, croupous pneumonia, erysipelas).



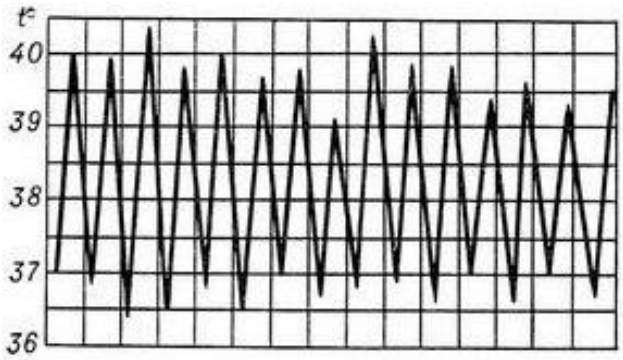
Febris remittens – daily fluctuation exceeds the 1° C range, the temperature does not return to the normal value (infectious diseases).



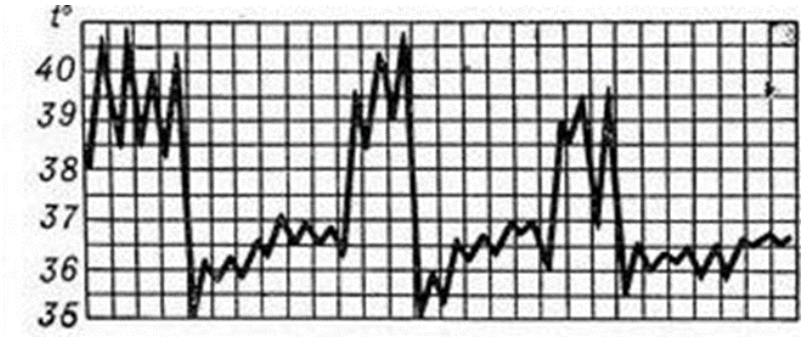
Febris intermittens - temperature swiftly raises to 39° C, swiftly falls below 37° C, in 24-hour period the difference of the maximum and minimum temperatures is bigger than 1° C (infectious endocarditis). Malaria, Borrelia, Schistosomiasis are examples of diseases where an intermittent fever curve can be observed. Malarial infections are especially recognisable for their distinct fever curves. Depending on the species of Plasmodium causing the infection, the periodicity of the intermittent fever can be every 24 hours (quotidian pattern - P.falciparum), 48 hours (tertian pattern - P.ovale and P.vivax) or 72 hours (quartan - P.malariae).



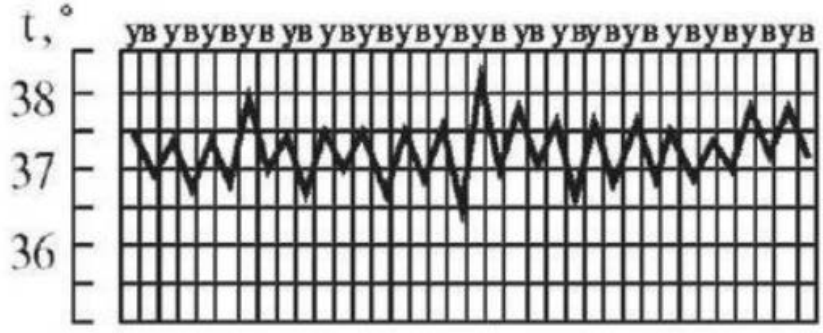
Febris hectica – refers to a pattern characterized by sharp swings in temperature - dramatic spikes of up to 3°C followed by periods of chills and profuse sweating. Most commonly seen in active pulmonary tuberculosis and sepsis.



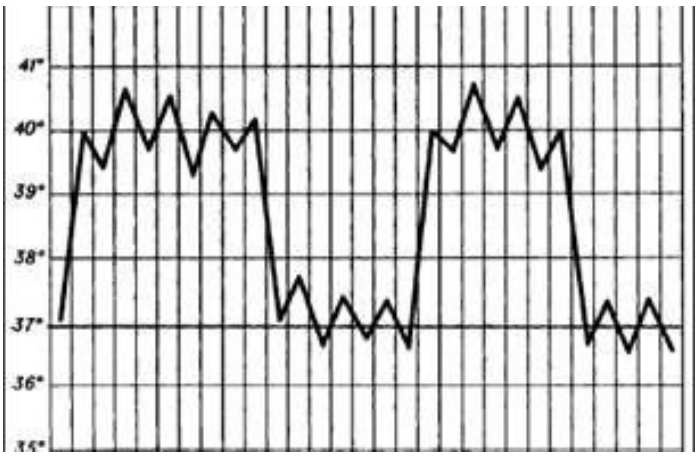
Febris recurrens – alternation of fever and apyretic periods of various duration (malaria). It refers to a fever pattern characterized by three or more episodes of febrile illness (fever) in a six-month period, each occurring at least 1 week apart, with no obvious underlying illness. This fever pattern is often seen in children.



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

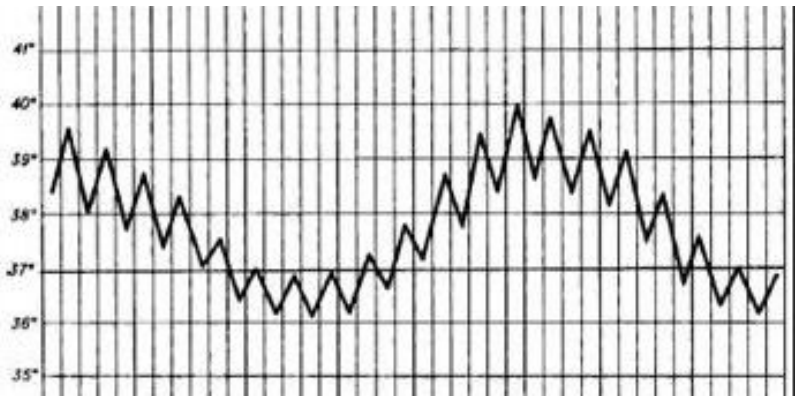


Febris irregularis or irregular fever refers to a fever pattern that has an irregularly fluctuating curve. There are no regular patterns in such curves. Such fever curves are extremely common among children and can be seen in diseases such as chronic bronchitis and rheumatism.



Febris undulans or undulating fever refers to a temperature curve characterised by gradual rises in temperature followed by gradual decreases, subsequently followed by an afebrile period until the fever begins again.

This type of curve is characteristic of infections caused by some species of Brucella (Brucellosis).



According to the degree of temperature increase, we can also define the next types of temperature:

Subfebrile temperature doesn't exceed 38^0 C; it accompanies local infections (chronic tonsillitis or sinusitis, urinary infections, adnexitis).

Febrile temperature (low grade fever) – temperature 38-39^0 C.

Pyretic temperature – from 39^0 to 41^0 C.

moderate grade fever 39.1– 40^0 C

high grade fever 40.1–41.0^0 C

Hyperpyretic fever (hyperpyrexia) – body temperature is higher than 41^0 C.

Temperature descent stage (stadium decrementi) is characterized with the decrease of pyrogenic cytokines synthesis which results from eliminating and destroying of the infectious and non-infectious primary pyrogens. Heat regulation center converts to the previous state; adjusting point falls to the normal physiological level. Surplus warm, which was accumulated in the organism, is lost owing to skin vessels dilation, abundant sweat secretion and breath speed-up. 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 pulse and respiration is decreased. Sudden decrease, especially of long-lasting fever, may cause temperature crisis, which is characterized with an acute decrease in peripheral vascular resistance. Such situation may cause the failure of circulation - collapse. This is especially dangerous for persons with CVS disease, aged persons.

ALTERATION OF METABOLISM AND BODY FUNCTIONS IN FEVER

The development of fever is accompanied by typical changes of metabolic processes: for each degree Celsius body temperature rise basal metabolic rate increases by 10 to 13 percent. This results in activation of oxidative processes and body’s requirement for oxygen increases.

The CO_2 content in arterial blood decreases (in the 2^{nd} stage of fever) due to increased alveolar ventilation. The consequence of hypocapnia is vasospasm of the blood vessels of the brain, deterioration of its oxygen supply.

Changes in carbohydrate and fat metabolism are associated with disorders of the sympathetic nervous system, accompanied by increased breakdown of glycogen in the liver and increased lipolysis. The glycogen content in hepatocytes decreases and there is a slight increase in blood glucose; sometimes patient with fever may have glucosuria. The mobilization of fat from the depot and its oxidation, which is the main source of energy in patients with fever. At the same time, there may be incomplete oxidation of fatty acids and increased formation of ketone bodies may occur. There is an activation of proteolysis in the muscles and a decrease in protein synthesis under the influence of cortisol, the secretion of which increases. In case of infectious fevers, a negative nitrogen balance may be detected. In addition to increased protein breakdown, this is facilitated by reduced intake of protein from food due to anorexia. Increased lipolysis and proteolysis lead to a decrease in body weight in case of prolonged fever.

Water-electrolyte metabolism is also changed. In the second stage of fever, water and sodium chloride are retained in the tissues, that is associated with increased aldosterone secretion. At the final stage the excretion of water and NaCl from the body is increased (in urine and sweat). In chronic fever, chloride metabolism is not disturbed. The development of fever is accompanied by a decrease in the concentration of free iron in the blood serum, at the same time, the content of ferritin increases. In case of prolonged fever, the following may occur an iron deficiency state may develop, which may result in mental depression, hypochromic anemia, and constipation. The basis of these disorders is a decrease in the activity of respiratory enzymes. The free content of serum and other bivalent cations (Si, Zn) due to increased binding by proteins of the "acute phase", which are synthesized by the liver in increased quantities during fever are synthesized by the liver in increased amounts to provide antimicrobial action.

The febrile state may be accompanied by shifts in the acid-base state: in moderate fever, gas alkalosis (due to hypocapnia), and in case of high fever metabolic acidosis.

Function of organs and systems during fever

Fever causes a number of changes in the functioning of organs and systems.

Nervous system function is affected with the pyrogens action that results in insomnia, high irritability, high sensitivity of skin and mucous covers, disturbances of reflexes. Delirium and sometimes hallucinations are common in high fever, loss of consciousness is possible, and children may develop convulsions. A frequent clinical symptom of fever is headache. These disorders are more common observed in infectious fever. As already mentioned, fever excites the centers of the sympathetic nervous system, which causes a number of changes in the functions of various organs.

The function of the cardiovascular system changes too. There is an increase in the frequency of heart rate it increases by an average of 8-10 beats for each degree of increase in body temperature. In children, tachycardia is more pronounced:

- the heart rate increases by 10 beats for every 0.5 °C increase in body temperature.

The minute heart volume increases by an average of 27%. Changes in cardiac activity in fever is caused by both the excitation of the sympathetic nervous system and the direct effect of high temperature on the sinus node. Some patients with an acute rise in body temperature develop arrhythmia. An overload form of heart failure may developed in high-grade fever. Blood pressure rises slightly in the first stage of fever (there is a spasm of skin vessels to reduce heat transfer), in the second stage it becomes normal or decreases by 10-15% compared to the norm (therefore, skin vessels dilate to increase heat transfer). In the third stage of fever, blood pressure is reduced or normal. In case of critical drop in body temperature, acute vascular failure (collapse) may develop. There may be microcirculatory disorders in the lung stasis, congestion. Blood pressure in the pulmonary artery often increases in due to constriction of its branches.

Breathing may be somewhat slow in the first stage of fever and accelerated in the second stage, which contributes to an increase in heat loss. These changes are explained by the effect of hyperthermia on the bulbar respiratory center.

Excretory system. In the first stage of fever, diuresis increases. This is due to increase in blood pressure due to spasm of skin vessels and outflow of a significant of blood to the internal organs, including the kidneys. At the second stage of fever, diuresis is reduced, which is mainly due to water retention and sodium in the tissues (increased secretion of aldosterone) and increased evaporation of water from the surface of the hyperemic skin and mucous membranes of the respiratory tract. In the third stage of fever, diuresis increases again, and with a critical drop in temperature due to a sharp increase in sweating and hypotension, diuresis decreases. Sometimes it develops albuminuria develops, and hyaline cylinders appear in the urine.

Significant changes occur with fever in the **gastrointestinal tract.**

Decreased salivation causes dry mouth, the epithelial cover of the of the lips dries and cracks, and a coating appears on the tongue. This creates conditions for the reproduction of various microorganisms (streptococci, staphylococci, spirochetes, etc.) in the oral cavity that causes specific unpleasant breath odor. These disorders require rinsing the mucous membrane of the mouth and pharynx with disinfectant solutions or wiping the lips and mouth with wet gauze moistened with these solutions. Patients are thirsty, and their appetite decreases. The secretion of gastric, pancreatic and intestinal juices ceases too. All above mentioned leads to digestive disorders. There is a need to feed febrile patients with easily digestible high-calorie foods (broths, juices, etc.). Stomach motility and its emptying are suppressed, that may cause vomiting. The motor function of the intestines is also reduced, and constipation develops as a result. Stagnation in the intestines in combined with a decrease in the secretion of digestive juices, contributes to the intensification of fermentation and putrefaction, the development of autoinflammation and flatulence.

Endocrine system directly participates in fever pathogenesis that is manifested with the blood level increase of certain hormones: ACTH, TSH, catecholamines, thyroid hormones and insulin. Fever is accompanied by the

development of stress. In this regard the production of ACTH and glucocorticoids increases. Excitation of the sympathetic nervous system is accompanied by an increased intake of catecholamines. In addition, fever increases the secretion of aldosterone and growth hormone.

Biological role of fever

Fever is considered mainly as a formed in the process of evolution a protective and adaptive reaction of the body to the action of various pathogenic factors. At the same time, like inflammation and other typical pathological processes, can have both positive and negative effects on the body.

The protective and adaptive value of fever is confirmed by the following facts:

1) fever enhances the body's immune response due to activation of T- and B-lymphocytes, acceleration of the latter's transformation into plasma cells, which stimulates the formation of antibodies; increased formation of interferon;

2) even a moderate degree of body temperature rise can activate the function of phagocytic cells and NK cells (natural killer cells);

3) enzymes that inhibit viral reproduction are activated;

4) slows down the reproduction of many bacteria and reduces the resistance of microorganisms to drugs;

5) the barrier and antitoxic functions of the liver increase;

6) sweat secretion and diuresis increase lead to more active excretion of toxic substances;

7) fever is often the first and only sign of a disease, an alarm signal.

Temporary increase of body temperature stimulates metabolic processes in cells and their functional activity. Blood supply of inner organs, particularly of the liver increases. It promotes the increase of its barrier function, protein and vitamin synthesis in it.

As a result, protein synthesis in the liver is altered: synthesis of C-reactive protein, serum amyloid A, fibrinogen, other clotting factors, hepcidin, haptoglobin, ceruloplasmin, anti-clotting factors: proteins C, S, antithrombin, plasminogen, protease inhibitors (α1-antitrypsin), components of the complement system, and

ferritin are increased. Most of these proteins are usually present in plasma in small amounts, and C-reactive protein and serum amyloid A are virtually absent outside the acute phase. An increase in these acute phase response proteins is accompanied by a decrease in albumin and transferrin synthesis. The latter are called negative (negative) acute phase proteins. Due to the decrease in albumin, increase in globulins and fibrinogen, dysproteinemia and increase in ESR develop. In acute injury, the concentration of C-reactive protein and serum amyloid A in the blood significantly increases already 6-10 hours after the injury. Concentrations of other proteins increase more slowly over 24-48 hours. Since the amount of C-reactive protein increases rapidly in the early stages of infectious and non-infectious inflammatory diseases and decreases rapidly during recovery, it is therefore a rather striking, albeit non-specific, criterion for assessing the course of inflammatory disease and the effectiveness of treatment. High level of C-reactive protein is a risk factor for myocardial infarction in patients suffering from coronary artery atherosclerosis.

Acute phase proteins are involved in many processes that maintain homeostasis. They have:

1. antimicrobial effects, e.g. complement components, C-reactive protein, serum amyloid;

2. antioxidant effects, e.g. haptoglobin, ceruloplasmin, ferritin, etc.;

3. pro-inflammatory and anti-inflammatory effects.

The negative impact of fever on the body is mainly manifested in the following cases when the body temperature rises acutely and remains for a long time. It is associated with stimulation of heart function, which can lead to the development of overload form of heart failure, especially in elderly and senile people, as well as in patients who have previously had a heart disease. There is a risk of collapse with a critical drop in body temperature in the final stage of fever.

In case of high fever, immune reactions can be suppressed.

It has been established that moderate fever increases the survival rate of infected animals, and excessively high fever increases mortality. In children with high fever, convulsions may develop, which are not always eliminated by taking

antipyretic drugs. At temperatures above 41 °C, children may develop cerebral edema or acute circulatory failure due to due to water-salt metabolism instability. Patients with prolonged fever (in tuberculosis, brucellosis, sepsis) are usually in a state of severe exhaustion and weakening of vital functions that is explained not only by high temperature, but also by the influence of microbial toxins.

HYPERTHERMIA AND THERMOTHERAPY

Body temperature increase can also take place without the presence of endogenous pyrogens. The temperature increase in these cases is called *hyperthermia.*

Hyperthermias are divided into exogenous and endogenous types according to their etiology and pathogenesis.

Exogenous hyperthermia takes place under considerable heat inflow increase: in the hot climate, hot workshops, under artificial air temperature increase in bath-houses, etc.

The causes of exogenous hyperthermia are factors disturbing heat irradiation – damp-proof heat-isolated clothes, high air humidity, insufficient ventilation. Exogenous hyperthermia develops quickly under the combination of hot surroundings with disturbances in heat irradiation. Under these conditions the heat irradiation mechanisms are not able to prevent to external heat inflow and body temperature increases.

Endogenous hyperthermia develops when excessive heat is produced in the organism itself. Endogenous hyperthermias can be divided into 3 groups:

1. Hyperthermia caused by alteration of thermoregulation center activity (not caused by pyrogens) develops due to:

• injury of thermoregulation center as a result of brain trauma, inflammation, edema, hypoxia, or microcirculation disturbances in hypothalamus;

• activation of stimulative influence of cerebral cortex on thermoregulation center under hysteria, psychical diseases, which are accompanied by nervous

excitation, strong emotion, stress, under psychoactive drugs (Coffeinum, Phenaminum).

2. Hyperthermia resulting from heat production increase, without alteration of thermoregulation center activity. Such kind of hyperthermia may occur as a result of:

• contractive thermogenesis increase (intensive muscular work in combination with conditions, disturbing the heat loss);

• pathological contractive thermogenesis – tetanus spasms, convulsions, strychnine injection and etc;

• disconnection of oxidation and phosphorylation processes in mitochondria with the increase of free heat formation (poisoning by 2,4-dinitrophenolum, hyperthyroidism).

3. Hyperthermia, caused by decreased heat loss without alteration f thermoregulation center activity:

• sweat secretion decrease under poisoning by cholinolytic medicines (Atropinum);

• spasm of skin vessels (adrenomimetic overdose and adrenalin increased synthesis).

Hyperthermia development usually develops in two stages: the stage of compensation and the stage of decompensation.

The compensation stage is characterized with activation of adaptive body mechanisms aimed to prevent overheating. The following mechanisms are directed to increase the heat loss:

• dilation of skin arterioles, increase of skin temperature;

• increased sweating;

• rapid breathing, fast, weak pulse (tachycardia).

The patient feels uncomfortable, exhausted, weakness, vomiting, headache and dizziness may occur; skin is flushed and red. Profuse sweating may result in dehydration.

Changes in body functions depending on the degree of temperature rise are as follows:

38°C - Sweating, feeling very uncomfortable, slightly hungry.

39°C - Severe sweating, flushed and very red. Fast heart rate and breathlessness. There may be exhaustion accompanying this. Children and epileptics may be very likely to get convulsions at this point.

40°C - Fainting, dehydration, weakness, vomiting, headache and dizziness may occur as well as profuse sweating.

If the adaptive mechanisms cannot maintain body temperature on the normal level and surrounding is still very hot, the **stage of decompensation** occurs. Patient may turn pale or remain flushed and red, skin is hot and dry, sweating may decrease. Accompanying dehydration can produce nausea, vomiting, headaches, and low blood pressure and the latter can lead to fainting or dizziness.

41°C - Fainting, vomiting, severe headache, dizziness, confusion, hallucinations, delirium and drowsiness can occur. There may also be palpitations and breathlessness.

42°C - Subject may turn pale or remain flushed and red. They may become comatose, be in severe delirium, vomiting, and convulsions can occur. Blood pressure may be high or low and heart rate will be very fast.

43°C - Normally death, or there may be serious brain damage, continuous convulsions and shock. Cardio-respiratory collapse will occur.

44°C or more - Almost certainly death will occur; however, patients have been known to survive up to 46°C.

A neuro-muscular vicious circle is formed at this stage. Extremely high body temperature increases the neuro-muscular excitability. That results in convulsions and increase of contractive thermogenesis. The latter potentiates the increase of body temperature and further increase of neuro-muscular excitability.

The disturbance of thermoregulation is the main feature of this stage. It manifests in disturbances of the CVS function, occurrence of acidosis, hypohydration and metabolic violations.

Hyperthermic cardiovascular syndrome is characterized with progressive tachycardia, decrease of heart stroke volume, development of microcirculation disorders and increased blood clotting.

Acidosis occurrence is determined by hypoxia development in the overheated organism. The increase of body temperature increases the speed of biochemical reactions. In this situation, body's requirement for oxygen increases (fast breathing) and accumulation of suboxidized products of metabolism occurs.

Hypohydration is the result of profound sweating. Loss of 10% volume of water leads to severe disturbances of vital functions. Ions of Na, K, Cl, Ca and others are lost with sweat. The important result of water loss is the increase of blood viscosity, which furthermore impairs the functions of cardiovascular system.

The biochemical effects of prolonged exposure to 42 o C can be fatal to the human body. Protein denatures, affecting all enzyme pathways; lipid membrane liquefies, destroying cell walls; mitochondria are damaged, paralyzing energy production. Peroxidative oxidation of lipids significantly increases that result in accumulation of high toxic suboxidized lipid metabolism products.

As the cell membrane is heated, the leak of Na + increases and the sodium–potassium pump is forced into overtime, effectively draining the cell of its energy store. Carbohydrate metabolism and other energy pathways are disrupted. The loss of energy in the cell induces its malfunction, allowing the overall storage of heat to accumulate and regulatory systems to fail. The end result is the increase of core temperature leading to the continuum of heat exhaustion and heat stroke.

The difference between fever and hyperthermia

Fever is a controlled increase in core temperature, associated with an increase in the hypothalamic thermostat set point in in response to a physiological threat. Fever is a part of the temperature response, characterized by a cytokine-mediated

rise in core temperature accompanied by an increase in acute phase agents and a host of other immunological, endocrine and physiological changes. Whereas, hyperthermia is an unregulated increase in core temperature in which inflammatory cytokines play a minimal role.

Hyperthermia is associated with disorders in the control of thermoregulation and is characterized by a steady increase in core temperature with no daily fluctuations characteristic of both normal body temperature and fever; does not respond to fever; it does not respond to antipyretic drugs.

Fever is usually caused by primary pyrogens (bacterial lipopolysaccarides, products of tissue decay) and is developed under the influence of secondary pyrogens. Hyperthermia develops without pyrogens influence.

Fever can develop only in homeothermic animals in comparison with hyperthermia. Nevertheless, ability to develop fever appears usually at the end of the first year of life when temperature homeostasis of the child is well-balanced. Children of the 1st year of life with infectious process are very frequently prone to hyperthermia.

The main link of pathogenesis in fever is the change of the thermoregulatory center adjusting point – thermoregulation of the organism functions normally, but temperature level is higher than normal. Hyperthermia in its turn is characterized with impaired thermoregulation.

Fever symptoms are dependent on the stage of its development. The symptoms of hyperthermia are the same from the beginning to the end of this pathological process, but their severity increases with time.

Taking into account the biological role of fever and hyperthermia for the organism, we should note that fever is a typical pathological process with both protective and damaging properties, while hyperthermia is extremely pathological.

Such differences in pathogenesis mean that the treatment of these two states should be different. Treatment of hyperthermia includes only physical methods of cooling.

Taking into account positive and negative fever effect on the body, the question of about the usefulness of antipyretic drugs cannot be resolved unambiguously. In addition to the previously mentioned data on the positive role of fever, one should the fact that its artificial suppression can make it difficult to diagnosis and prediction of the severity of the disease. At the same time, it was found that the positive effect of fever on the development of the disease is only manifested in its moderate and short course. High fever causes suffering to the patient, adversely affects the cardiovascular system and the central nervous system, digestive processes, reduces the manifestation of a number of defense reactions, such as phagocytosis, antibody formation, etc.

The main indications for the use of antipyretic therapy should be considered:

- High and prolonged fever with a temperature rise of up to 39-40 °C;
- Moderate fever in patients with diseases of the cardiovascular system and other vital organs;
- Moderate fever in patients with acute neurological disorders;
- Moderate fever in the presence of shock, sepsis, severe metabolic disorders;
- Patients of elderly and senile age;
- Children under 5 years of age, especially if there is a history of seizures.

Nonsteroidal antipyretic drugs are used as antipyretic agents anti-inflammatory drugs (acetylsalicylic acid, paracetamol, amidopyrine, etc.), quinine, glucocorticoids and other medications.

Thermotherapy

We can use positive events occurring during body temperature increase with medical purpose. Such type of treatment, is called thermotherapy/pyrotherapy.

Thermotherapy or pyrotherapy may be used in two ways: general thermotherapy and local thermotherapy.

General thermotherapy is provided with injection of bacterial lipopolysaccaride in order to cause fever development. Moderate increase of body

temperature improves adaptive response of the organism and can be applied in the following cases:

• To intensify adaptive and innate immunity during chronic infectious diseases (post-infectious arthritis, syphilis, tuberculosis of bones).

• To intensify reparative processes in bones and other tissues after their damage, trauma, surgical operations.

Pyrotherapy

Pyrotherapy is a method of treating various diseases by artificially raising the temperature of the human body or inducing hyperthermia. Pyrotherapy was first used at the end of the 18th century, when fever was caused by the administration of various putrefactive products to animals (Seybert, 1798). Burdon-Sanderson (1876) prepared a fever-inducing drug from rotting meat by precipitation with alcohol, which he called pyrogen. In 1874, the chief physician of the Odesa Psychiatric Hospital, A.S. Rosenblum (the founder of the method of febrile-infectious therapy for mental patients), taking advantage of the typhoid epidemic that was raging in Odesa at the time, successfully inoculated 12 mental patients with this infectious-fever disease. Following the successful experiments of the Viennese psychiatrist Wagner-Jauregg on malaria vaccination for therapeutic purposes in chronically mentally ill patients, starting in the first quarter of the twentieth century, the method of malarial therapy was successfully introduced into psychiatric practice to treat brain syphilis patients, paraplegics, and patients suffering from schizophrenia. In addition to malarial therapy, intense febrile conditions caused by turpentine abscesses, sulphosinotherapy, etc. were introduced. Furthermore, pyrogenic drugs - lipopolysaccharides - were used in medical practice: pyromen, pyrexal, etc. A drug that has not lost its importance to this day is pyrogenal, prepared from microbial cultures of Pseudomonas aeruginosa and E. typhosa. Lipopolysaccharide has a complex structure, but its main components are lipoid A and a polysaccharide, which includes an O-specific chain and an oligosaccharide backbone. Immunization with lipopolysaccharides or gram-negative bacteria induces the formation of antibodies only to the O-specific chain of lipopolysaccharides, which has antigenic properties.

The activation of protective mechanisms under the influence of lipopolysaccharides is mainly associated with the polysaccharide; while the toxic effects are caused by lipoid A. Purified lipoid A has immunogenicity and can stimulate protective reactions, but this ability is weak in the whole lipopolysaccharides molecule. According to B.V. Kraitserov, pyrogenal can be considered as a nonspecific stressor that can be dosed and causes sanitogenic stress, mobilises and stimulates the body's defenses. Thus, pyrogenal as a sanitogenic stressor promotes adequate restructuring of reciprocal relations between sympathetic and parasympathetic tone at a new level. Firstly, lipopolysaccharide is used to stimulate immunity and nonspecific resistance of the body: at higher temperatures, the synthesis of antibodies, interferons, interleukins and other cytokines is more intense, a general increase in the intensity of oxidative metabolism and increased formation of free radicals toxic to microorganisms and parasites, increased leukopoiesis and the development of hyperleukocytosis, chemotaxis and phagocytic activity of leukocytes are observed. Immunostimulation is associated with the effectiveness of pyrotherapy in many slow-moving, chronic infectious diseases that normally occur without a temperature reaction, without severe inflammation and without the formation of a strained immune system. Secondly, the effectiveness of pyrotherapy in some diseases is associated with an increase in the permeability of blood vessels and tissue barriers not only to immune cells and humoral immunity factors, but also to antibiotics and other drugs. The increased permeability of the blood-brain barrier to antibiotics and chemotherapy is associated with the effectiveness of pyrotherapy in syphilitic encephalitis (progressive paralysis), CNS toxoplasmosis and other neuroinfections; for antidepressants and antipsychotics - in case of resistant depression and psychosis. The effectiveness of pyrotherapy in chronic prostatitis is associated with an increase in the permeability of the blood-brain barrier to antibiotics. Thirdly, the effectiveness of pyrotherapy is related to the properties of the pathogens of some diseases that cannot reproduce or reproduce poorly when the host's body temperature rises. For example, the effect of pyrotherapy for syphilis is also due to the high heat sensitivity of the pathogen. Pyrotherapy is also effective in the treatment of malignant

hypertension of renal origin, because the dilation of the abdominal vessels that occurs during its use causes an increase in blood flow in the kidneys and a decrease in overall blood pressure. Good results were obtained in the treatment of bone and joint tuberculosis. In recent years, the possibility of using pyrotherapy for cancer has been investigated, as the tumor necrotizing effect of a biologically active substance, tumor necrosis factor, which is produced in the body in significant quantities during fever, has been established. In addition, high temperature in some cases increases the sensitivity of tumors to chemotherapy and radiation. Thus, the multifaceted effect of lipopolysaccharides, their influence on the body's resistance and reactivity ensures the high efficiency of pyrotherapy in medicine.

Local thermotherapy, or therapy by induced localized hyperthermia, may be used for cancer treatment to kill or weaken the tumor cells, with negligible effects on the healthy cells. Tumor cells, with a disorganized and compact vascular structure, survive with a difficulty in a hot surrounding.

Hyperthermia may therefore cause cancerous cells to undergo apoptosis in direct response to applied heat, while normal healthy cells can more easily adapt to high temperature. It also causes braking of mitoses in cancer cells, denaturation of cancer cell membrane proteins. Even if the tumor cells do not die outright, they may become more susceptible to ionizing radiation treatments or to certain chemotherapies, allowing such therapy to be given in smaller doses.

HYPOTHERMIA AND MEDICAL HIBERNATION

Hypothermia is a medical condition in which the patient's core body temperature has dropped significantly below normal and normal metabolism begins to be impaired. This begins to occur when the core temperature drops below 35 degrees Celsius.

The reasons of hypothermia are:

- not effective thermoregulatory mechanisms (infants, babies and aged people);
- too long exposure to the cold surroundings;

- disturbances of nervous system function (drugs, alcohol, toxic substances, Parkinson disease);
- disturbances of endocrine system function (hypothyroidism, hypopituitarism adrenal insufficiency) that lead to decreased heat production.

There are two stages of hypothermia development: compensation stage and decompensation stage. At the stage of compensation, behavioral thermoregulation takes place: the patient tries to go out from the cold surrounding, put on more warm clothes and so on. Heat loss may be restricted by peripheral blood vessels constriction. Heat production is increased by the activation of bloodflow in inner organs, induction of contractive thermogenesis (shivering). The necessity to produce more heat provokes functional changes in the human organism: tachycardia, increase of AP and heart stroke volume, increased ventilation of lung. These changes form the conditions for basal metabolic rate activation, which is accompanied with the increase of heat production. These mechanisms can keep constant core temperature.

Changes in body functions depending on the degree of temperature decrease are as follows:

35°C - Intense shivering, numbness and blueish/greyness of the skin.

34°C - Severe shivering, loss of movement of fingers, blueness and confusion.

Nevertheless, if the temperature of the surrounding remains too cold compensatory abilities of the organism are exhausted and **decompensation stage occurs**:

33°C - Moderate to severe confusion, sleepiness, depressed reflexes, progressive loss of shivering, slow heartbeat, shallow breathing. Shivering may stop. Subject may be unresponsive to certain stimuli.

32°C Hallucinations, delirium, complete confusion, extreme sleepiness that is progressively becoming comatose. Shivering is absent (patient may even think they are hot). Reflex may be absent or very slight.

31°C - Comatose, very rarely conscious. No or slight reflexes. Very shallow breathing and slow heart rate. Possibility of serious heart rhythm problems.

28°C - Severe heart rhythm disturbances are likely and breathing may stop at any time. Patient may appear to be dead.

24-26°C or less - Death usually occurs due to irregular heartbeat or respiratory arrest; however, some patients have to been known to survive with body temperatures as low as 14°C.

The second stage of hypothermia slows chemical reactions, increases blood viscosity, slows blood flow, and increases blood coagulation. As the result tissue's hypoxia and inhibition of metabolism in the organism develops. Cold core temperature (below 25C) causes the depression of brain respiratory, vascular and thermoregulation centers, the violation of heart contraction.

Three vicious circles are formed during severe hypothermia: metabolic vicious circle, vascular vicious circle, neuro-muscular vicious circle.

Metabolic vicious circle. It is known that lowering of the body temperature in combination with hypoxia inhibits metabolic processes. Inhibition of the metabolism results in low heat production, which leads to lowering of the body temperature again.

Vascular vicious circle. Increasing lowering of the body's temperature is accompanied with the dilation of arterial vessels of the skin, mucous covers and subcutaneous layers. This phenomena is observed when body temperature is 30 -33 C and is determined by neurovascular mechanism. Dilatation of the vessels leads to increased heat loss, which results in more cooling.

Neuro-muscular vicious circle. Progressive hypothermia causes the decrease of neural centers excitability, namely of the neural centers which control muscle tonus and contraction. As the consequence contractive thermogenesis becomes impossible what leads to more cooling again.

Low blood temperature causes inhibition of the brain cortex and sub cortex structures. It manifests in apathy and extreme sleepiness that is progressively becoming comatose.

Hypothermia is dangerous, but at the same time, when the temperature decreases, the organism becomes more resistant to the damaging effects of external

or internal environmental factors. This fundamental property of therapeutic hypothermia in experiments makes it possible to stop blood circulation in chilled animals for 1-2 hours without subsequent deleterious effects. This remarkable difference between 4-5 minutes in normothermia and 2 hours in deep hypothermia has been a major factor in attracting many physicians and scientists to this field. The potential therapeutic and protective properties of hypothermia provided the basis for its introduction into practical medicine.

Controlled hypothermia **(medical hibernation)** may be of two variants: local and systemic.

Systemic controlled hypothermia is used in clinics in the surgical operations on the "dry" organs with stopped bloodflow – heart (congenital or acquired heart defects), brain, large vessels. Body's temperature is artificially decreased to 28-30^{0}C. Cells and tissues in the controlled hypothermia decrease their functional activity that results in low speed of metabolic processes, decrease of cell's oxygen consumption, decreased carbon dioxide production. It prevents disturbances of acid-base balance, water and ion metabolism, increase tissue's resistance to hypoxia and other pathogenic stimuli.

Local induced hypothermia of the single organs (brain, kidneys, liver, prostate and others) is provided when it is needed to carry out complex surgical operations.

The prospects of using medical hibernation are now working out by the scientists all over the world. Medical hibernation in future will be able to solve the following problems:

Organ preservation. A big problem in organ transplantation is time. Lacking fresh blood, even cooled organs quickly become unusable.

Stroke. Most strokes are caused by a blocked blood vessel to the brain, which starves brain cells. But the brains of hibernating animals somehow survive restricted blood flow. If this question will be answered it might buy stroke victims some time for survival.

Trauma. Soldiers in combat and gunshot victims often bleed to death from their wounds. Instead of focusing on increasing blood supply through transfusions scientists are looking for the ways of rapidly reducing the body's oxygen demand, potentially giving medics time to evacuate or treat the victim.

Direct human use of hibernators' secrets is years off, and it's unlikely that we'll ever regularly spend months in a state of extreme torpor. But our basic similarity to these animals is close enough to make their protective tricks theoretically applicable. Last year, scientists reported hibernation behavior in one species of lemur – a primate, like humans. It all adds to the promise that the outwardly simple process of hibernation will yield answers to some of medicine's most complex problems.

SELF-ASSESSMENT QUESTIONS
ON THE TOPIC “PATHOLOGY OF THERMOREGULATION”:

1. Normal thermoregulation mechanisms. Physical and chemical thermoregulation
2. Definition of fever. Etiology and types of fever.
3. The role of primary and secondary pyrogens in fever development.
4. What are the functions of pyrogenic cytokines?
5. What is the mechanism of temperature rise in stage 1 of fever?
6. What is chills? Pathogenesis of chills
7. What are the changes in heat production in stages 1, 2, and 3 of fever?
8. Does the temperature rise in fever depend on the ambient temperature?
9 Does the febrile organism retain the ability to thermoregulate?
10. What fever is called subfebrile, febrile, pyretic, hyperpyretic?
11. What are the types of temperature curves?
12. What changes in diuresis are observed in the different stages of fever?
13. What are the changes in cardiovascular function in fever?
14. What are the features of fat, protein and carbohydrate metabolism at different stages of fever?
15. Mechanism of protective action of fever.
16. What harmful effect can fever have?
17. Indications for the use of antipyretic therapy.
18. Hyperthermia: stages, mechanism of development.
19. The difference between fever and hyperthermia. Biological importance of fever
20. Hypothermia stages, mechanism of development.

SITUATIONAL TASKS

Task 1

Patient V., 32 years old had complaints about headache, weakness, muscle pains, stuffiness in nose in the morning. In 3 hours the temperature raised to 38,40C, heart rate – 98 bpm, breaths frequency – 26 per minute. Diagnosis: acute respiratory viral infection.

1. What is the source of the primary pyrogens in this case?
2. Explain the mechanism of increased heart rate, breaths frequency and the meaning of it.
3. Should this case of fever be treated with medicines? Why?

Task 2

Patient T, 47 years old, delivered to the hospital by ambulance complains of increasing pain behind sternum and in the epigastrical area during a day. During patient's examination were found: paleness of skin, increased sweating, acrocyanosis, body's temperature 37,6oC, ABP 100/65 mmHg, heart rate – 100 bpm. The analysis of ECG revealed acute myocardial infarction.

1. What is the cause of temperature increase in this case? Name the source of primary pyrogens.
2. Should this patient be prescribed antipyretic medicines? Why?

Task 3

Patient M., 52 years old. Diagnosis: bronchial asthma. Patient is treated with glucocorticoids. Fever reaction appeared as a result of post-injective abscess development. Subfebrile temperature didn't correspond to severity of inflammatory process.

1. Why patient has low fever reaction?
2. Which factor determines the level of body temperature increase in the fever?

Task 4

A child 5 years old spent several hours in the closed car which was staying under the sun. When the child was found his body temperature was 39,70C, heart

rate – 145 bpm, breaths quantity 33 per minute; he was wet of sweating and had single convulsions. The doctor prescribed a dropper with saline and adrenaline.

1. Define the pathology and stage of its development. Define the vicious circles in pathogenesis.

2. Explain the prescriptions of the doctor

Task 5

Patient T, 27 years old, was operated for mitral insufficiency. Systemic controlled hypothermia was conducted and his body's temperature was decreased to 34oC after narcosis. The operation on the dry heart, which lasted for 40 minutes, was effective.

1. Explain, why hypothermia was conducted to the patient?

2. Explain, why organism is less sensitive for intoxication, infection, hypoxia, and other injuries during hypothermia.

Task 6

In experiments on normal and tolerant to bacterial pyrogen rabbits the pyrogenic properties of blood sera obtained at different time intervals after intravenous injection of bacterial pyrogen into experimental animals were determined.

It turned out that injection of serum taken 5 min after injection of bacterial pyrogen into a rabbit leads to the development of fever with a long latent period in a normal rabbit and does not cause fever in a tolerant rabbit. In contrast, administration of serum taken 120 min after bacterial pyrogen injection results in the development of a febrile reaction in both normal and tolerant rabbits, with normal rabbits developing fever after a shorter latency period.

1. Why does serum taken 120 min after administration of a bacterial pyrogen have a pyrogenic effect when administered to tolerant rabbits, as opposed to serum taken 5 min after administration of a bacterial pyrogen?

2. How can we explain the shorter latent period of febrile reaction in normal animals compared to tolerant rabbits when serum taken 120 min after pyrogenal injection is administered to them?

PATHOGENESIS OF TUMOR GROWTH

MECHANISMS OF CELL PROLIFERATION CONTROL

Cell division (proliferation) is a physiological process that occurs in almost all tissues and under many circumstances. Normally, the balance between proliferation and programmed cell death (usually in the form of apoptosis) is maintained by tightly regulating both processes to ensure the integrity of organs and tissues.

Cells require highly specific proteins (growth factors) to stimulate and inhibit cell division. The main sources of these factors are macrophages, fibroblasts and liver cells. Several well known growth factors are: epidermal growth factor, endothelial growth factor, fibroblast growth factor, platelet-derived growth factor, nerve growth factor, insulin-like growth factors and others. Leukotrienes 1-7 are also known as cell growth activators. Platelet-derived growth factor stimulates the production of connective tissue cells; interleukin stimulates the proliferation of T cells. Cells bear specific membrane receptors for appropriate growth factors.

Tumor growth is always based on damage to the cell's genome.

Damage to the cell genome can occurs in three classes of regulatory genes:

1) genes that stimulate tumor cell division - protooncogenes;

2) genes inhibiting cell division of tumor cells – antioncogenes, (suppressor genes);

3) genes responsible for apoptosis.

Cellular proto-oncogenes

The genes which are controlling growth factors synthesis are named proto-oncogenes. If gene controlling growth factor is mutant or hyperactivated it may cause increased synthesis of the growth factors. Such gene is named oncogene. As a result uncontrollable cell division starts (tumor development).

During the study of viral carcinogenesis it was found that oncoviruses, when entering cells, introduce genes into the cell genome that stimulate and qualitatively disrupt cell proliferation and therefore promote cellular malignization. These genes

have been called viral oncogenes. Cytogenetic studies have shown that analogs of viral oncogenes are also present in human and animal cells, where they perform various regulatory functions regulation of synthetic processes and cellular division. Moreover, it is hypothesized that the viruses carrying these oncogenes once stole them from their host cells. Therefore, in order to better distinguish between cellular regulatory genes. (analogous to viral oncogenes) have been called proto-oncogenes, and in case of their overexpression (activation) - cellular oncogenes.

Cellular oncogenes appear at such damage to the genome of the cell, when the regulation of proto-oncogene functions is disturbed.

The reasons for such overexpression of genes or excessive activation of their protein-products may be the following:

Amplification - an increase (usually multiple) in the number of copies of proto-oncogenes, leading to activation of tumor cell transformation.

Translocation - as a result of moving a proto-oncogene located in one chromosome to a strong promoter region located in another chromosome, an inactive proto-oncogene is transformed into an oncogene.

Point mutation of a proto-oncogene can lead to altered metabolism and accumulation of its protein product.

Transduction - capture of cellular oncogenes by viruses and their "unblocking" in the virus genome under the influence of different promoters, which eventually leads to disorder of genetic regulation of cell division processes.

DNA demethylation - the demethylated DNA region that appears under the influence of chemical carcinogens and active radicals becomes active and leads to stimulation of cell division.

According to the mechanism of action oncogenes are divided into four main groups.

1. oncogenes encoding growth factors.

2. oncogenes encoding receptors to growth factors - membrane proteins with protein kinase activity. The theory of oncogenes assumes the formation of receptors with constant high activity, i.e. independent of stimulation by growth factors.

3. oncogenes encoding signal transduction in the cell cytoplasm, such as those associated with the G-protein system.

4. oncogenes encoding nuclear proteins involved in DNA transcription and replication.

Antioncogenes, or tumor suppressor genes

Their role in carcinogenesis is well established by studying hereditary tumors. It is known that many hereditary tumors are known to be associated with mutations in certain genes, leading to a loss of their function and the emergence of tumors. These genes have been called as anti-oncogenes. This group of genes have different functions in the cell.

Some genes suppress tumor development - their protein product inhibits mitosis. They are called tumor suppressor gene or anti-oncogenes. Oncogenes and tumor suppressor genes take part in the development of tumors. The development of tumor involves inactivation of tumor suppressor genes and activation of oncogenes.

Genes regulating apoptosis (responsible for programmed cell death). Since one of the main properties of a tumor is its immortalization, changes in the activity of genes affecting apoptosis are of great importance in this process. The P-53 gene (information is given above), Bsl-2, Bsl-x and some other genes are recognized as the main ones in this family. Depending on the functions of the proteins encoded by these genes, different disorders are necessary for tumor development. First, if proteins (e.g., p53) trigger apoptosis, "switching off" the genes encoding these proteins is necessary for tumor development. Secondly, if proteins-products of these genes prevent cell apoptosis (like Bsl-2 and Bsl-x), then overexpression of such genes in cells results in a marked lengthening of their lifespan, which promotes tumor development.

Thus, proto-oncogenes under the action of carcinogens mutate into oncogenes that encode the production of oncoproteins as a result of altered cell properties. Oncoproteins participate in the processes of transcription, translation and DNA replication. It has been shown that it is not enough to activate carcinogenesis only by enhancing the activity of cell division stimulator genes. For this purpose, it is

necessary that cell division inhibitor genes are suppressed. In addition, it is also necessary that genes regulating cell apoptosis are also repressed (damaged).

It should be noted that in a tumor cell there is not a single, but multiple disruption of the genome and, as a rule, there is activation of several oncogenes and "switching off" the functions of several anti-oncogenes. The step-by-step damage of the cell genome leads to its malignization - tumor progression. Thus, tumor progression occurs when the functions of many genes with different localization in the genome are disturbed.

TUMOR ETIOLOGICAL FACTORS

Carcinogenesis (the process of tumor development) may occur due to gene mutation – **mutational carcinogenesis** or without mutation – **epigenetic carcinogenesis.**

A **carcinogen** is a substance, organism or agent capable of causing cancer. Carcinogens may occur naturally in the environment (such as ultraviolet rays in sunlight and certain viruses) or may be generated by humans (such as automobile exhaust fumes and cigarette smoke). Most carcinogens work by interacting with a cell's DNA to produce mutations.

Carcinogens are agents of various origins that:

- cause tumors that do not develop spontaneously;
- increase the incidence of spontaneous tumors;
- increase the multiplicity of spontaneous tumors or significantly shorten the latency period for their appearance.

Physical carcinogens cause the development of human tumors in about 10% of cases (if we take 100% of all carcinogens as their occurrence). They include excessive solar radiation, ultraviolet rays, and, mainly, various ionizing radiations: X-rays, neutron, α-, β- and γ-rays, protons, natural and artificial radionuclides, including technological and medicinal isotopes and preparations.

Excessive solar radiation and, mainly, ultraviolet rays can penetrate into the cell-tissue structures of the epidermis, have mutagenic effect on them and eventually

lead to the development of tumors (mainly melanomas, sarcomas, cancer) in them. Thus, it is known that in southern areas skin cancer accounts for 20-25% of all forms of cancer, and in northern areas - only 4-7%.

Under the influence of various photosensitizing (including perfumes and cosmetics), as well as chemical carcinogens mutagenic effect of ultraviolet rays and solar radiation is greatly enhanced.

Ionizing radiation has a powerful penetrating and mutagenic effect. There is a selective sensitivity of cells to radiation. The most sensitive tissue is considered hematopoietic: several years after general irradiation sharply increases the incidence of leukemia. Very sensitive to the effects of radiation thyroid gland and mammary glands. Known cases where women with pulmonary tuberculosis and because of this frequent fluoroscopic examinations, became ill with breast cancer. Of great importance is the age at which exposure to radiation: the maximum incidence of breast tumors noted after radiation damage received at the age of 10-20 years. When exposed at a younger or older age, the risk of developing these tumors decreases.

Chemical carcinogens cause tumors development in humans in about 80% of all neoplasms.

Chemical carcinogens may be of exogenous and endogenous origin. Exogenous carcinogens of industrial, medicinal, household, food and other origin include:

- Polycyclic aromatic hydrocarbons (PAHs): 3,4-benzpyrene, dibenzpyrene and their derivatives, etc.);

- amino compounds (4-nitroquinoline-N-oxide, etc.);

- aromatic amino compounds (benzidyl, 2-naphthylamine, etc.);

- aromatic azo compounds (paradimethylaminoazobenzene, orthoamino-azotoluene, etc.);

- nitroso compounds (nitrosamines, nitrosamides: N-nitroso-dimethylamine, N-nitrosomethylurea, etc.);

- aflatoxins (aflatoxin B1, safrole, etc.);

- other organic and inorganic substances (polyethylene, asbestos, epoxides, aldehydes, beryllium, cobalt, arsenic, cadmium, lead, nickel, etc.).

In decreasing ability to cause malignant tumors, a variety of exogenous factors can be arranged in the following order: 1) food factors; 2) tobacco; 3) occupational hazards; 4) infectious factors; 5) environmental pollution; 6) alcohol; 7) diagnostic tools, etc., in descending order.

Thus, long-term consumption of foods rich in carbohydrates, fats, table salt, smoked meats, pickles on the background of lack of proteins, fresh fruits and vegetables sharply increases the risk of cancer of the stomach, pancreas, colon, especially rectum and prostate.

Smokers have an 11 times higher mortality rate for lung cancer and a 7 times higher mortality rate for cancer of the pharynx, larynx and esophagus than nonsmokers. Smoking also increases the risk of developing tumors of the liver, pancreas, bladder, and other organs.

Endogenous carcinogens include cholesterol and its derivatives (steroid hormones, especially estrogens, and bile acids), derivatives of tyrosine, tryptophan and other amino acids, free radicals, peroxides and others. In an experiment on mice it was shown that the administration of large doses of estrogens causes the development of mammary cancer in these animals. The role of bile acids as endogenous carcinogens can be proved by the high frequency of colon cancer in people whose diet includes a large amount of fats (fats stimulate the formation and secretion of bile, and bile acids contribute to the damage of the mucous membrane of the colon and the development of tumors).

By chemical nature, carcinogens are divided into organic and inorganic. Classification by initial carcinogenic activity - into indirect carcinogens (pre-carcinogens; acquire carcinogenic properties only after metabolic transformations in cells, for example, after their oxidation by monooxygenase enzyme system of cells of different tissues and organs) and direct carcinogens; by mechanism of action - genotoxic (damaging the cell genome) and epigenetic (not affecting the cell genome).

Biological carcinogens (mainly viruses) cause about 10% of all cancers in humans.

The main role is played by oncoviruses (from Greek oncos - tumor, Lat. virus - poison). Their size ranges from 40 to 220 nm. They contain DNA or RNA and are covered with a protein shell (capsid). Oncoviruses after interacting with membrane receptors, lose their capsids and and enter the cell as a nucleotide. Here they multiply by replicating nucleic acid followed by capsid synthesis and self-assembly into a virion. There are over 150 known oncoviruses.

Many mutagens are also carcinogens, but some carcinogens are not mutagens. These are thought to promote cancers through their stimulating effect on the rate of cell mitosis. Any event that stimulates the rate of mitosis can lead to epigenetic transformation of the cell. **Epigenetic transformation** refers to those processes which cause normal cells to become tumor cells without the occurrence of any mutations. In this case we observe epigenetic carcinogenesis.

Faster rates of mitosis increasingly leave fewer opportunities for reparative enzymes to repair damaged DNA during DNA replication. Such effect is peculiar to:

- certain hormones (e.g., estrogens that stimulate mitosis in the breast);
- chronic tissue injury (which increases mitosis in the stem cells needed to repair the damage);
- agents that cause inflammation (which generates DNA-damaging oxidizing agents in the cell – ROS produced by neutrophils);
- certain viruses.

Host factors (gender, hormones, aging) and environmental factors may have a modifying role in increasing, or decreasing the susceptibility to carcinogens. Microsomal enzymes in the liver degrade (detoxify) a large part of a pro-carcinogens (substances that can convert to carcinogens) to non-carcinogenic products. A variety of naturally occurring compounds, such as indole, flavones, and related compounds that occur in vegetables have a protective action in animals exposed to carcinogenic polycyclic hydrocarbons.

Endogenous (and exogenous) sex hormones are important factors apparently at the promotion stage of some human carcinomas. Breast, endometrium, and prostate carcinoma bear receptors for sex hormones, therefore high level of androgen, estrogen and progesterone increase the mitotic rate of the epithelial cells in the tumor and in the organ concerned. High mitotic rates can increase cancer risk by increasing the chance of mutations occurring and of being replicated before they are repaired, and can also increase the growth of early tumors. Treatment with hormones' antagonists improves prognosis for these patients.

The role of heredity in the development of tumors

In humans, up to 10% of tumors can be attributed to hereditary factors. For example, such rare tumors as familial retinoblastoma, familial adenopolyposis of the colon, neurofibromatosis, and some others are transmitted in the dominant type. By recessive type are transmitted such rare in the population tumors such as breast cancer, colon cancer and others.

It is known that tumors often occur in different generations in members of the same family ("cancer family"). Most often this type of inheritance is found in families with defects in genes responsible for genome stability, as a result of which DNA repair is impaired, various cellular mutations occur (spontaneously or under the influence of external factors), which can very quickly lead to the development of tumors. Quite often tumors develop in various clinical forms of immunodeficiencies.

In animals, the role of hereditary factors in tumor development is much better studied than in humans. Even certain lines of animals with certain hereditary tumor diseases have been bred.

Precancerous conditions

The term "precancer" is understood as "a pathological condition characterized by the prolonged coexistence of atrophic, dystrophic and proliferative processes, which precedes the development of malignant tumor and in a large number of cases with increasing probability of transition into it".

Specifically, precancerous conditions include the following:

- Chronic proliferative inflammatory processes and diseases accompanied by phenomena of intense proliferation (overgrowth of cell-tissue structures), dystrophy and atrophy (specific examples are chronic gastritis, gastric and duodenal ulcers, cervical erosions, etc.);

- hyperplastic processes and diseases accompanied by the development of foci of cellular hyperplasia, more often of glandular tissue, without phenomena of tissue and cellular cataplasia (a specific example may be cystic-fibrotic mastopathy, etc.);

- benign tumors (papillomas, adenomas, fibromas, lipomas, myomas, osteomas, gliomas, nevi), which under the influence of various carcinogens can transform into malignant tumors (cancer in situ, cancer, adenocarcinoma, sarcoma, glioblastoma, melanoma, etc.).

Some precancerous conditions, characterized by hereditary predisposition, are always malignant (malignant) - the so-called obligatory precancer. Others do not always turn into malignant tumors - the so-called facultative (optional) precancer.

GENERAL CHARACTERISTICS NEOPLASM

The process of cancer or other tumor development is named carcinogenesis. There are three stages of carcinogenesis:

Stage 1. Initiation (transformation). A single cell in a tissue suffers a mutation in a gene involved in the cell cycle (protooncogene or tumor suppressor gene). This results in giving this cell a slight growth advantage over other dividing cells in the tissue; the normal cell is transformed to a tumor cell. It can stay in such a state for a long time without dividing, but possessing a potential possibility for unlimited growth.

Stage 2. Promotion. The promotion stage is considered to be a relatively lengthy and reversible process. Transformed cell under the effect of promoters begins to multiply, giving the beginning to the clone – progeny of cells. Promoters are compounds that bind to receptors on the cell surface and promote its proliferation; not obviously carcinogenic. Examples for tumor promoters are estrogens with respect to mammary carcinoma, androgens for prostate cancer. The

proliferative stimulus by a chronic ulcer may have a tumor promoter effect in the development of gastric cancer, and regenerative proliferation in chronic viral hepatitis may promote development of hepatocellular carcinoma. The primary tumor node which consists of similar cells forms as a result of this stage (carcinoma in situ).

Stage 3. Tumor progression.

As this cell develops into a clone, some of its descendants suffer another mutation in another cell-cycle gene. This further deregulates the cell cycle of that cell and its descendants. As the rate of mitosis in that clone increases, the chances of further DNA damage increases. New mutation affect tumor cells, making them more malignant. Regulatory systems of the organism (immune, endocrine, etc.) affect the multiplying tumor cells. Those tumor cells that are less subjected to the effect of host organism regulatory systems are in more profitable conditions and will multiply more actively. Natural selection takes place among the multiplying tumor cells.

Eventually, so many mutations have occurred that the growth of that clone becomes completely unregulated. Tumor tissue obtains polymorphism (consists of different cellular clones that differ from each other), increases the speed of its growth, and obtains malignant character.

There are two types of neoplasms: **benign** and **malignant**. Benign and malignant neoplasms have both similar and distinctive features.

Characteristics Shared by Benign and Malignant Neoplasms

1. I**rreversible new growth**. Once a cell is transformed into a neoplastic one, it never will be normal again. Growth controlling mechanisms present in normal cells are permanently impaired in neoplastic cells. The expression “active, progressive growth” applies both to benign and malignant neoplasia. It differs from hyperplasia that is also characterized by cellular proliferation, but once its cause is removed, cell growth stops.

2. **Absence of cell division limit**. Normal cells have a division limit, i.e. is genetically programmed capability to divide only certain amount of times. This theory was worked out by **Dr. Hayflick** who established that the human cells ability

to divide is limited to approximately 50-times, after which they simply stop dividing (and hence die). This phenomenon is known to be triggered as a result of shortened telomeres. Cancer cells have the ability to overcome this limit by using mechanisms capable of maintaining telomere lengths (such as expressing telomerase), which enables cancer cells to divide indefinitely. Therefore, tumor cells are theoretically immortal. The doubling rate of benign cells is relatively slow. The growth rate is much faster in malignant neoplasms.

3. Inadequate differentiation in comparison with normal cells. Normally differentiation is the process of specialization. By specializing, cells acquire special functions — muscle cells contract, gland cells secrete, and nerve cells conduct. Neoplastic cells do not become as specialized as normal cells. The more differentiation is displayed by neoplastic cells, the more likely the neoplasm is benign; the less differentiation displayed by neoplastic cells, the more likely the neoplasm is malignant. Benign neoplasms are composed of cells that more closely resemble normal, mature, adult, differentiated cells. Malignant neoplasms are composed of the cells that more closely resemble primitive, immature, juvenile, undifferentiated, stem cells. Such loss of cells' differentiation and their orientation to one another is termed **anaplasia**.

Anaplasia types

The term **anaplasia** means "to form backward," which implies dedifferentiation (or loss of the structural and functional differentiation) of normal cells during tumorigenesis.

The more anaplasia is observed, the more malignant a neoplasm is; the less anaplasia is observed the less malignant is a neoplasm.

There are several types of anaplasia: morphological, biochemical, physical, chemical, functional.

Morphological anaplasia is a reliable index of cancer diagnosis. Cancer cells can differ from healthy cells by the following features:

- Variety of sizes and shapes – a property known as **polymorphism** or **pleomorphism**. The more polymorphism is present, the more anaplastic is the tissue.

- Increased nuclear/cytoplasmic ratio - abnormally large nucleus with irregular nuclear contours.
- Abnormally dark nuclei – hyperchromatism.
- Enlarged and multiplied nucleoli.

Biochemical anaplasia is characterized by the disturbance of all kinds of metabolism in the tumor cell: carbohydrate, protein, lipid, nucleic. The most important for diagnosing is **carbohydrate atypia** – the disturbance of carbohydrates metabolism which is displayed by shift to anaerobic glycolysis and negative Paster's effect. In the norm Paster's effect is positive in the presence of oxygen and results in decomposition of carbohydrates to carbon dioxide and water. In malignant cells, in spite of oxygen presence, the secretion of great amount of sub-oxidized products occurs, particularly, lactic acid, that gets into blood and decreases the surface tension and viscosity of blood**. Protein atypia** is the disturbance of protein metabolism and is characterized by the synthesis of unusual proteins in certain kinds of tumors. The presence of these proteins, also called embryonic proteins (alpha-fetoprotein), is a diagnostic test for hepatoma identification.

Immunologic (antigenic) anaplasia. The antigenic composition of malignant tumors clearly differs from normal tissues. In particular, the following types of tumor antigens are found in them.

- Tumor antigens induced by the action of various carcinogens. As a result of mutations caused by carcinogenic factors, tumor cells can synthesize proteins with antigenic properties. They are strictly individual and are characterized by polymorphism depending on the type of carcinogens (antigenic complexity).

- Viral tumor antigens. When tumors are induced by the same virus, these antigens are the same for several tumors both in the same individual and in different individuals (antigenic simplification).

- Embryonic antigens. These include proteins (e.g., α-fetoprotein, cancer-embryonic antigen, etc.) that result from antigenic reversion (appearance of antigens peculiar to distant ancestors).

- Heterorganic antigens. In part of cases, especially in immunosuppression,

antigens characteristic of other organs can be found in tumors of some organs (antigenic divergence).

Tumor tissue usually escapes the strict, characteristic of healthy tissues, immune surveillance. This occurs because of:

1) reduction of tissue-specific and individual antigens with preservation of species-specific antigens (to the latter every organism of the same species has immunological tolerance, i.e. tolerance, insensitivity);

2) appearance of embryonic antigens;

3) masking of tumor antigens from immune surveillance, for example, as a result of formation of blocking antibodies, coating of tumor cells with fibrin film or development of immune suppression (secondary immunodeficiency).

Functional anaplasia. Normal cells stop their division when they contact surrounding cells, and that is called **contact inhibition**. Tumor cells do not stop their division even when they contact the surrounding cells. Thus, they destroy healthy cells and grow into the surrounding tissue. Malignant neoplasms of non-endocrine origin can excrete ectopic hormones Certain lung cancers produce antidiuretic hormone (inducing hyponatremia in the patient), adrenocorticotropic hormone (resulting in Cushing syndrome), parathyroid-like hormone or calcitonin (both of which are implicated in hypercalcemia), gonadotropins (causing gynecomastia), serotonin and bradykinin.

Autonomy (independence from the **organism**) means that tumor cells with their boundless growth get out of control of regulating systems of the organism (nervous, endocrine, immune). However, these systems save partial (relative) control over the tumor tissue, which gives doctors the opportunity to treat the patient with the help of these systems.

Loss of polarity and specialized functions. As cells become more specialized during normal development, they form highly organized relationships with other similar cells. Simple columnar epithelial lining membranes are one example of such a highly organized tissue. These membranes are always one cell thick, their nuclei are always located at the end of the cell resting on the underlying connective tissue,

and their intracellular organelles are always located in certain locations within the cell—they are polarized cells. Since anaplastic cells are not as differentiated as normal ones, anaplastic cells have less polarization and possess fewer specialized functions. The more severe the anaplasia, the more polarity and specialized functions are impaired.

Differences between benign and malignant neoplasms

Benign neoplasms do not penetrate (invade) adjacent tissues as they grow; they compress them. This growth pattern is known as expansive growth. As compression occurs, a demarcation line is formed between surrounding tissues and the neoplasm. Sometimes a fibrous connective tissue enhances this demarcation. It happens, because during expansive growth of benign tumor the focus of inflammation is formed around it – tumor cells are alien to the host body and the organism tries to destroy them or if they can't be destroyed – separate these alien cells from the normal tissues. This separation is provided with the help of connective tissue proliferation and capsule formation. At surgery, the demarcation allows the removal of the tumor without much surrounding damage. When they arise from some surface (e.g. the lining of the mouth), benign neoplasms almost always grow outward from the surface –a pattern known an exophytic growth.

Benign neoplasms never metastasize. Benign neoplasms are composed of well-differentiated neoplastic cells that resemble the tissue from which they originated; anaplasia is absent. Hence, a lipoma is composed of mature fat cells that contain cytoplasmic lipid vacuoles. Likewise, a chondroma is composed of mature cartilage cells that synthesize their usual cartilaginous matrix. Cells of benign neoplasms stay attached to each other, they do not wander off. Because of their cohesiveness, they do not enter blood or lymphatic vessels to metastasize.

Malignant neoplasms in their turn grow rapidly and have the capacity to invade surrounding tissues damaging them with the help of proteolytic enzymes. Because of this invasive growth pattern, they are not well demarcated from the surrounding tissues. If they arise from some surface, malignant neoplasms grow inward invading the underlying tissues; this pattern is called endophytic growth.

Frequently even after complete surgical resection of primary malignant tumor it can appear again. Such event is termed tumor relapse. It can occur because malignant tumors are difficult to eradicate and even single malignant cell that remained may start to grow.

Metastatic malignant neoplasms cause severe body wasting – **cachexia** (loss of weight, muscle atrophy, fatigue, weakness and anorexia). Cachexia is often seen in end-stage cancer, and in that context is called "cancer cachexia".

Table 1. Summary of differences between benign and malignant tumor

	Benign	Malignant
Level of differentiation	Lower than normal	Very low
Autonomy	Low	Very high
Structure	Resemblance to normal cells	Abnormal; less similarity to normal cells
Type of growth	Expansive, exophytic	Invasive, endophytic.
Metastasis	None	Frequent
Effect on host	Slight harm, due to location or complication	Significant harm, due to invasion and metastasis
Possibility of relapse	Does not give relapses.	Gives relapses
Cancer cachexia	Only in case of peculiar location (in esophagus)	Present
Encapsulation	Present	Does not have a capsule

Invasion and metastasis of malignant tumor cells

Malignant cells possess the ability to break away and enter surrounding tissues, a feature known as “invasion.” To invade, malignant cells must lose their attachment to their neighbors and secrete substances that dissolve surrounding ground substance and collagen fibers. As malignant cells invade, they encounter, infiltrate, and overwhelm important structures – nerves, ducts, bone marrow, and others. Finally, invasive malignant cells can invade lymphatic and blood vessels providing ready access to body regions far from their point of origin.

The tendency of malignant neoplasms to spread far is called metastasis (meta- = change, -stasis = location). The term “metastasis” is only used in reference to malignant neoplasms. The presence or absence of regional and, particularly, distant metastasis is a major factor in determining the prognosis of a malignant neoplasm. Conceptually, metastasis involves three steps or processes:

Tumor cell invasion. In the process of tissue invasion by an epithelial cancer, tumor cells must traverse the barriers of the basement membrane and the stromal extracellular matrix. Tumor cells detach from the primary tumor due to decreased mutual adhesiveness, diminished number of cell junctions, and other alterations in surface membrane structures. Then they have to degrade the basement membrane components, and subsequently the stromal extracellular matrix. The enzymatic breakdown of proteins and proteoglycans is accomplished in various ways. Tumor cells can produce plasminogen activator, a serine protease that splits plasminogen into its proteolytically active form, plasmin, or collagenase (which can cleave basement membrane collagen). In some tumors, proteolytic enzymes are released in the stroma by "cooperating" host cells, such as macrophages. Then cancer cell move deeper into the region where the matrix has been broken down and finally invade lymphatic or blood vessels.

Tumor cell embolization (migration, transport). Malignant tumor cells may invade lymphatic or blood vessels and enter the circulation, but only small number of embolized cells are apparently able to establish metastatic lesions. Tumor cell invasion of blood, or lymphatic, vessels is not sufficient by itself to establish metastatic tumor growth.

The next step **is tumor cell extravasation**. Cancer cell attaches to the endothelial surface, induces endothelial retraction, migrates through the “holes” between endothelial cells, dissects the endothelium, degrades the vascular basement membrane, and migrates out of the vascular compartment to form a metastatic tumor.

Malignant tumor cells may spread by three major routes: lymphatic vessels, blood vessels, and implantation (seeding) by physical contact between tumor and normal serosal or mucosal surfaces.

ANTI-TUMOR DEFENSE AND TUMOR-HOST INTERRELATIONS

Mechanisms of anti-tumor defense

Activation of oncogenes, carcinogenes influence and even appearance of tumor cell do not obviously lead to the tumor development. Tumor growth is possible only when mechanisms of anti-tumor defense are not effective in fighting against the tumor. There are anticarcinogenic, antimutational and anticellular mechanisms of anti-tumor defense.

Anticarcinogenic mechanisms provide braking of carcinogen entrance in host cells and its organelles, their inactivation and elimination from the human organism. They include:

• Binding of the chemical carcinogen with the necessary substances in order to form constant compounds which can be eliminated from the organism with sweat, urine, bile, faeces and saliva;

• Inactivation of carcinogens by phagocytosis;

• Activation of anti-oxidative system (prevention of free radicals mutative influence);

• Inactivation of carcinogens by the natural metabolic processes (oxidation, reduction, sulfating and other reactions);

• Carcinogenic virus infected cells can be recognized and destroyed by immune cells: cytotoxic T-lymphocytes, natural killers.

If anticarcinogenic mechanisms failed carcinogens induce oncogenes activation. Their activation is prevented by antimutational mechanisms.

Antimutational mechanisms provide revealing, elimination or inhibition of oncogene activity with the help of tumor suppressor gene (anti-oncogenes) or DNA reparative systems.

If antimutational mechanisms failed and oncogenes were activated the normal cell turns to tumor one. This event serves as a signal of anticellular mechanisms switching on.

Anticellular mechanisms provide the recognition and destruction of tumor cells or inhibition of their proliferation. Anticellular mechanisms are supported with

immune and none-immune mechanisms .

Non-specific immune mechanisms include both cellular and humoral factors. Phagocytes and natural killers can kill tumor cells. The most widely known humoral factor is tumor necrosis factor alpha (TNF). TNFα is released primarily by WBC and endothelium. It has a number of influences on various organ and systems:

On the hypothalamus:

• Stimulating of the corticotropin releasing hormone release;

• Suppressing appetite (hence its synonym "cachexin");

• Altering of thermoregulation “set point” and causing fever.

On the liver: stimulating the acute phase response, leading to an increase in C-reactive protein, proteinase inhibitors (antitrypsin, antichemotrypsin), coagulation proteins (fibrinogen, prothrombin, factor VIII, plasminogen), complement proteins,

Oncolytic effect of TNF is provided due to its ability:

• To attract neutrophils very potently and help them to stick to the endothelial cells for migration.

• To stimulate phagocytosis and activate “respiratory burst” in phagocytes.

• To activate thrombogenesis in the vessels of tumor that leads to its ischemia and further necrosis.

Specific immune mechanisms are represented by cellular immunity (cytotoxic T-cells or T-killers) and humoral immunity (specific antibodies). Immune anti-cellular mechanisms include all links of the immune system that prevent tumor development by destroying mutated cells with the help of:

1) natural killer (NK) and cytotoxic T-lymphocytes, which have a high degree of cytotoxicity towards tumor cell (foreign);

2) phagocytes (monocytes, tissue macrophages, neutrophils, neuroglial cells) that perform phagocytosis of tumor cell antigens, presentation of these antigens to T-helper cells, formation of interferons (α, β, γ), tumor necrosis factors;

3) antitumor antibodies;

4) complement system factors, etc.

Nonimmunogenic anticellular mechanisms inhibit the growth of tumor cells

by creating unfavorable conditions for their growth, preventing tumor metastasis, etc. For example, heparin and components of the fibrinolytic system prevent the formation of fibrin films around tumor cells and hematogenous metastasis of these cells, etc. Nonimmunogenic mechanisms in antitumor defense are less important than the immunogenic.

However, despite the presence of a system of immunogenic and non-immunogenic mechanisms to protect the body from constantly forming tumor cells, some of them (about 0.01%) escapes from immune surveillance and spreads throughout the body with extracellular fluid, blood and lymph. Malignant tumor cells escape from immunologic control successfully with the help of the following:

- low immunogenicity of tumor antigens;
- constant modification of tumor antigens;
- clonal selection of immune resistant tumor cells;
- expression of embryonic antigens;
- absence of MHC molecules (low differentiation of tumor cells);
- resistance to apoptosis;
- depression of immune system by producing specific inhibitory cytokines.

In such cases, more frequent development and sharply pronounced acceleration of growth, invasion and metastasis of tumors, as well as the development of a variety of (including infectious) complications are noted.

Interrelations between the host organism and the tumor

All tumors, even benign ones, may cause morbidity (disease occurrence) and mortality (death occurrence). Obviously, cancers are far more threatening to the host than benign tumors. Nonetheless, both types of neoplasia may cause problems because of location and impingement on adjacent structures, functional activity such as hormone synthesis, and the production of bleeding and secondary infections when they ulcerate through adjacent natural surfaces. Any metastasis has the same potential. Cancers may also be responsible for cachexia (wasting) or paraneoplastic syndromes.

Location is of critical importance with both benign and malignant tumors. A

small (1 cm) adenoma in hypophysis can compress and destroy the surrounding normal gland and give rise to hypopituitarism. A comparably small carcinoma within the common bile duct may induce fatal biliary tract obstruction.

The production of hormones is seen with both benign and malignant neoplasms arising in endocrine glands. The adenoma or carcinoma arising in the beta cells of the islets of the pancreas often produces hyperinsulinism, sometimes fatal. In the same way, tumors of the adrenal cortex elaborate corticosteroids (for example, aldosterone, which induces sodium retention, hypertension, and hypokalemia).

Ulceration through a surface with consequent bleeding or secondary infection needs no further comment. The neoplasm, benign or malignant, that protrudes into the gut lumen may get caught in the peristaltic pull to telescope the neoplasm and its site of origin into the downstream segment of gut— intussusception— leading to ulceration of the mucosa or, even worse, intestinal obstruction or infarction.

Cancer (tumor) cachexia (kachexia from Greek kacos - bad, hexis - condition) is caused by hypo- and anorexia that develops during the progression of tumor growth. The latter develops as a result of: 1) disruption of the activity of the food motivational center, as well as taste receptors and other links of the taste analyzer; 2) nausea, vomiting, diarrhea; 3) activation of catabolic processes in non-tumor tissues, etc., as a result of tumor growth progression.

All this is due to the action of toxic metabolites, decay products of tumor tissue, various antitumor drugs, as well as increased formation of various cytokines by macrophages and other cells of the body (especially TNFα, capable of causing cachexia in high concentrations, and therefore received the second name "cachectin").

Immunosuppression, often noted in tumor growth, may be realized with the participation of the following mechanisms.

Carcinogen-induced immunosuppression. Many carcinogenic factors cause not only damage to the cell genome, but are also capable of suppressing the immune system. The strongest immunosuppressive effect has radiation, ultraviolet irradiation, viral infection, as well as chemical carcinogens.

Tumor-induced immunosuppression. Often tumor cells synthesize various cytokines (βTGF, etc.) that disrupt the fine regulation of the immune response and lead to the development of immune failure.

Hormone-induced immunosuppression. In tumorigenesis, the intensity of glucocorticoid formation is usually increased. This is due to the metabolic features of the tumor "as a trap" glucose, which leads to hypoglycemia, hence - to the stimulation of glucocorticoids gluconeogenesis.

Immunosuppression caused by cancer cachexia. Immune suppression leads to a high incidence of infectious and toxic complications, as well as the development of autoimmune reactions.

Blood system disorders at different stages of tumor disease can be very different. Anemias develop more frequently, in particular, the following:

- Posthemorrhagic (due to bleeding from tumors, etc.);

- hypoplastic (as a result of suppression of erythropoiesis due to intoxication, defi- cit of erythropoietin, folic acid, compression of the erythroid sprout of the bone marrow by granulocytes intensively formed in the white sprout under the influence of TNFα, IL-1);

- hemolytic (due to the formation of autoimmune reactions, as well as the decay of red blood cells as they pass through the capillaries of tumor tissue, especially its central part, which is in a state of hypoxia).

It is possible, although more rarely noted, the development of erythrocytosis due to increased formation of erythropoietin in tumors (especially in renal carcinomas, liver) and ectopic foci (in hemangioblastomas of the cerebellum, adrenal tumors, uterus, lung).

Tumors often develop leukocytosis (usually neutrophilic and / or monocytic), which is due to excessive formation of cytokines by macrophages in response to the action of tumor antigens (TNFα, IL-1, etc.).

It is also possible to develop leukopenia, which is more often associated with the appearance and growth of metastases in the bone marrow, liver, spleen, etc.

Thrombocytopenia often develops due to the growth of metastases in the bone

marrow, increased breakdown of platelets or due to increased consumption of platelets by microclots (in the case of DIC).

Disorders of hemostasis are usually manifested by hypercoagulation (resulting from excessive release of thromboplastin by developing tumor cells), as well as a decrease in thromboresistance and increase in thrombogenic properties of vascular walls, which is accompanied by the development of migrating venous thrombosis.

It is possible and the development of hypocoagulation (arising, as a rule, due to coagulopathy of consumption in DIC or the development of thrombocytopenia).

Disturbances of the microcirculation system are usually caused by nonspecific effects on the endothelium of microvessels of the products of decay and metabolism of the tumor, as well as a large number of cytokines formed (especially in the endothelium). This is accompanied by an increase in the microvessels of various organs endothelial adhesiveness, aggregation and agglutination of blood form elements, vascular permeability, as well as the activity of mast cells, edema, dystrophic processes in tissues, etc.

Disorders of histohematic barriers are caused by various (endocrine, neurological and autoimmune) disorders.

Endocrine disorders (endocrinopathias) are a classic paraneoplastic process if they are caused by the occurrence of an ectopic focus of secretion of certain hormones. The main types of endocrinopathies that contribute to the development of the paraneoplastic process include the following:

- Cushing's syndrome. It is usually associated with a hormonally active adrenal tumor, but occasionally occurs with ectopic secretion of ACTH or ACTH-like peptide. It's not uncommon for this syndrome develops in lung cancer as well as in ovarian, thyroid, pancreatic, and other cancers.

- Carcinoid syndrome. Carcinoid is a tumor originating from APUD cells. In 85% of cases the tumor is localized in the gastrointestinal tract, in 10% - in the lung, in 5% - in other organs. The main substances secreted by carcinoids are serotonin, kinins and intestinal peptides (hormones): gastrin, vasoactive intestinal polypeptide (VIP), somatostatin and others. When these substances are overproduced,

cardiovascular system disorders (changes in blood pressure, etc.) and gastrointestinal tract disorders (hypersecretion of gastric juice, diarrhea, hypokalemia and metabolic alkalosis) occur.

- Hypercalcemia of paraneoplastic origin can develop in breast, lung, kidney, and other cancers with the participation of various mechanisms: osteolysis (occurring in 10-20% of patients with tumor metastasis to bone), ectopic formation of parathormone, excessive formation of TNFα, prostaglandin E2, and stable metabolites of vitamin D. All these factors activate osteoclasts, bone resorption processes and the development of osteoporosis.

- Neurologic disorders of paraneoplastic genesis occur in about 7% of various cancer patients. They concern various "departments" and links of the nervous system (somatic and autonomous; central and peripheral). More often, such disorders are found in lung, breast, ovarian, and gastric cancer. In the genesis of neurological disorders may be important as autoimmune processes, as well as the formation and action of toxins and biologically active substances. One of the most important neurological disorders is pain associated with the involvement of nerve fibers in the tumor process and the action of biologically active substances (prostaglandins, kinins, etc.) on nerve endings.

Basic principles of tumor prevention

Regular and thorough medical examination. Mandatory periodic ultrasound examinations (ultrasound) of internal organs and fluorography of the thoracic cavity.

Adherence to an active healthy lifestyle, ensuring the preservation and preventing the weakening of the body's defense mechanisms and reactions, including the following:

- optimization of everyday life, nutrition, work, rest, psycho-emotional state of a person;

- elimination or reduction of bad habits (especially pathological motivations), chronic stress (distress), hypodynamia (hypokinesia), immunodeficiency and other risk factors for neoplasms;

- reducing the possibility of various (especially chronic) traumatizations,

intoxications, infections, ionizing irradiation, etc.;

- activation of weakened antioxidant, anticoagulant, fibrinolytic, antimutagenic, immune and other regulatory and life-supporting executive systems;

- prevention of disorders and early normalization of disturbed metabolic processes (lipid, carbohydrate, protein, including enzyme, as well as vitamin, electrolyte, water and other types of metabolism), etc.

Basic principles of tumor treatment

Simultaneous or sequential use of local, regional and general, mainly pathogenetic (substitutive, stimulating, inhibitory and corrective), sanogenetic and symptomatic treatment.

Traditional main methods of treatment of human tumors are methods by means of which removal or destruction of tumor tissue under the action of chemical or physical factors takes place. The most commonly used method is surgery (radical and palliative surgeries).

When surgical removal of tumors, such as hemoblastosis, is impossible, the main method of treatment becomes a medical method. It includes the use of various groups of antitumor drugs: antitumor antibiotics, alkylating, antimetabolic, hormonal drugs, etc. These drugs, possessing various mechanisms, have different mechanisms. These drugs, having different mechanisms of action, are designed to inhibit the processes of division and growth of tumor cells.

An important method of radical treatment of tumors is the method of radiation therapy. For this treatment, high doses of radiation (X-rays, cobalt and other radiation) are used. With good focusing of these rays on the tumor, tissue there is suppression of growth and death of tumor cells.

Often a combination of different methods is used to improve the effect of treatment. Most often surgical, drug and radiation treatment methods are combined. In this case, the drug method becomes an auxiliary or adjuvant method.

Recently, immunologic and genetic methods of treatment have become a separate direction in antitumor therapy. These methods are very promising, have a

high degree of specificity of action against tumor cells, but are complex and often very expensive.

The main immunological methods of tumor treatment include the following.

- Treatment with adapted cells (activated with IL-2) T-lymphocytes, NK and others.

- Treatment with monoclonal anti-tumor specific antibodies.

- Treatment with cytokines to stimulate the immune response (IL-2, α-IF, etc.), increase antitumor immunological resistance (TNFα), restore impaired cell differentiation (recombinant retinoic acid preparations, etc.).

Genotherapy methods include delivery to tumor cells:

- Antioncogenes, the loss of which has pathogenetic significance in tumor development. Thus, viral vectors are used to deliver genes p16, p53, Rb1 and some others. This leads to partial correction of the cell genome damage;

- viral vectors of genes that inhibit cellular hyperexpressed genes (oncogenes).

In addition to treatment methods mainly acting to reduce the number of tumor cells, we can use a variety of adjuvant drugs, the effect of which is aimed at:

- demasking of malignant tumor cells (by eliminating the fibrin film on their surface, which isolates these cells from the body's immune surveillance system);

- activation of weakened cellular and humoral, specific and nonspecific links of immunity;

- inhibition of the formation of microvessels feeding tumor tissue;

- normalization of energy and plastic metabolism in tumor tissue and in the whole organism (by prescribing antihypoxants, antioxidants, adaptogenic, detoxifying and numerous other means, as well as systemic and local hyperthermia, local hyperoxygenation and hyperglycemia, etc.);

- stimulation of antitumor resistance of the organism and other methods.

SELF-ASSESSMENT QUESTIONS
ON THE TOPIC “PATHOGENESIS OF TUMOR GROWTH”:

1. Which genes are controlling cell growth?
2. What is the role of proto-oncogenes and antioncogens in tumor development?
3. Specify the role of heredity in tumor development.
4. What are the main types of carcinognes in humans?
5. What is the difference between mutational and epigenetic carcinogenesis?
6. Describe the precancerous states.
7. Describe the stages of tumor development.
8. What are the common characteristics of benign and malignant tumors?
9. What are the features of morphological anaplasia?
10. What are the features of biochemical anaplasia?
11. What are the features of antigenic anaplasia?
12. What are the features of functional anaplasia?
13. Describe the differences between benign and malignant neoplasms.
14. What are mechanisms of development of invasion and metastasis of malignant tumor cells?
15. Which types of anti-tumor defense are possible?
16. How does tumor cell escape immune control?
17. Describe the interrelations between the host organism and the tumor.
18. What is the origin of cancer cachexia, immunosuppression and blood disorders in the patient with malignant tumors?
19. Name the basic principles of tumors prevention and treatment.
20. Which modern methods of tumor treatment are possible?

SITUATIONAL TASKS

Task 1

Patient R., 52 years old, complains of weakness, abdominal pain, digestion disorders, and 40% weight loss. Laparotomy: pancreas tumor with metastases in mesentery of intestines, liver and spleen. Carbohydrate, protein and lipid metabolisms disorders were found. Blood analysis: hypoglycemia, hyperlipidemia, hyponitrogenemia, negative nitrogen balance.

1. What are possible mechanisms of cancer cachexia in this patient?
2. Explain the mechanism of hypoglycemia, hyperlipidemia, hyponitrogenemia, negative nitrogen balance.
3. Which type of growth is typical for this tumor? Explain the mechanism of it

Task 2

Patient G., 35 years old. Leukemia was found in 3 months after he has got a 7 Gy dose of ionizing radiation. He has 15 kg weight loss, there are a lot of hemorrhages of different size on the skin. Roentgenogram revealed double-sided pneumonia.

1. What is a possible mechanism of patient’s tumor development?
2. What is cell division limit (Hayflick’s limit)? How does it change in tumor cells?
3. Is the any interrelation between leukemia and pneumonia? Explain it.

Task 3

Patient E. Breast tumor without pain was found, skin around it wasn’t hyperemied, skin temperature is normal. Histology research: tumor is in capsule, there is no inflammation around the tumor, expansive growth, tumor cells are equal in size and form, tumor metastases in other organs and tissues were not found.

1. Which type of tumor does the patient have? Prove your answer.
2. Explain the mechanism of capsule formation.
3. Is relapse possible in this type of tumor?

Task 4

Cells clone was cultivated in vitro (in Petri dish). If oxygen is added, lactate is secreted, if glucose solution is added, glucose concentration in the clone equals to 0.

1. Determine the character of cellular clone, which was cultivated in the experiment.

2. Which type of anaplasia is described? Which other types of anaplasia do you know?

3. What was a cause of glucose absence and lactate formation in the cellular clone?

Task 5

The patient with malignant tumor of the thyroid gland was treated with cytostatic drugs. The treatment limited growth of the cells in the primary tumor node, but not in metastases.

1. Define the stage of tumor development in the patient.
2. Why malignant tumors are able to give metastases?
3. Why cells of tumor metastases are more resistant to anti-tumor therapy?

Task 5

One of the modern approaches to tumor treatment is photodynamic therapy based on the combined use of drugs - photosensitizers and low-intensity laser radiation with a wavelength corresponding to the absorption peak of the photosensitizer. The accumulation of photosensitizers in atypical cells and tumor tissues leads to the death of these cells after exposure to radiation.

1. What kind of damage to proteins, lipids, and nucleic acids of cells can be observed during photodynamic therapy.

2. Explain the mechanisms of cytostatic and cytolytic effects of photodynamic therapy.

3. What principles of tumor therapy do you know?

RECOMMENDED LITERATURE

1. Pathophysiology : textbook for students of higher medical educational institutions of the III-IV accreditation levels / N. V. Krishtal [et al.] ; ed. by.: N. V. Krishtal, V. A. Mikhnev. – 3rd ed., corrected. - Kyiv : AUS Medicine Publishing, 2020. - 670 p.

2. General and Clinical Pathophysiology : textbook for students of higher educational institutions, of IVth level of accreditation / A. V. Kubyshkin [et al.] ; ed. by.: A. I. Gozhenko, Lukasz Szarpak. – 5th ed. - Vinnytsya : Nova Knyha Publishers, 2021. - 696 p.