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GENERAL PATHOLOGY

TYPICAL PATHOLOGIC PROCESSES

PART 1

Manual
for third year students
of medical colleges
of higher education

ФЕДЕРАЛЬНОЕ АГЕНТСТВО ПО ЗДРАВООХРАНЕНИЮ
И СОЦИАЛЬНОМУ РАЗВИТИЮ

ВОЛГОГРАДСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

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"GENERAL PATHOLOGY. TYPICAL PATHOLOGIC PROCESSES"

Part 1.

(manual for third year students of medical colleges of higher education)

Рекомендуется Учебно-методическим объединением по медицинскому и фармацевтическому образованию вузов России в качестве учебного пособия для иностранных студентов медицинских вузов, обучающихся на английском языке

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"General pathology. Typical pathologic processes" Part 1. (Manual for third year students of medical colleges of higher education.)

The Subject and Objectives of Pathophysiology

Doctrine of Etiology and Pathogenesis

Fever

The manual contains lectures, tests & situational tasks, in the following subjects: the subject and task of pathophysiology; doctrine about etiology and pathogenesis; pathogenesis fever This division is for the third year students of the medical institutions working on their own or with a teacher.

Approved by the Central methodic council of the Volgograd Medical State University.

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The Subject and Objectives of Pathophysiology

Theory of Etiology and Pathogenesis

Pathological physiology is the science of vital functions of a sick organism.

The course of pathological physiology consists of three parts:

The first part is nosology or a science of diseases. When a doctor analyzes a disease he has two questions in mind. The first question is why a disease has started and the second how it is developing.

The second part includes typical pathological processes. It includes information about processes, which underlie numerous pathological processes (inflammation, fever, tumor, etc.).

The third part deals with particular pathophysiological problems. In this part students study separate organs and systems: blood circulation, respiration, nervous system and et cetera.

The tasks of nosology.

Nosology deals with many problems: building basic scientific terms, used in medicine: Health and Disease, pathological processes, conditions, pathological reactions, stages of a disease, its complications, and other terms which are of medical importance.

- Development of nomenclature of diseases and their conditions.
- Building a classification of diseases.
- Laying the foundations for the general study of diseases.
- Developing a theoretical conception of medicine.

Basic concepts of nosology:

Health, disease, normal, pathological reaction, pathological process and pathological conditions.

Disease: In medicine the term 'disease' is used in two meanings.

In its main meaning the term denotes a specific disease (e.g. pneumonia, gastritis, anemia, hypertonic disease). In this meaning the term 'disease' denotes a definite disease which can develop in a certain person in a specific nosological

form (the type of a disease is determined according to its ethiology, the mechanism of its development and as well as its symptoms).

The second meaning of the term Disease is used to refer to a condition which is different from a healthy state. It denotes a specific form of the living organism, a specific biological phenomenon.

There is no precise definition of the notion 'disease'. Various definitions of this condition given by different authors reflect a number of essential general characteristics distinguishing this condition from a healthy one.

A disease is a disturbance of the normal activities of the organism. It is a specific condition different from a healthy one.

There are some quantitative parameters (e.g. breathing rate, heart beat, blood pressure, body temperature, etc.) and qualitative characteristics which differ a sick organism from a healthy one. A sick body starts to react to the agents it used to be unresponsive to before. For example, a patient with bronchial asthma can develop an acute condition under the effect of flower pollen, grass, trees or animal wool. Yet, some patients have not experienced this type of reaction before.

- A disease develops when hereditary defects in the genetic programme are realized and or when the organism is affected by any stimulants.

This indicates that each disease has its own cause.

- A disease is a process developing according to certain laws.

For example, a hypertonic disease and its varieties involving disturbances of endocrine, renal, vascular and other mechanisms regulating blood pressure develops as a result of impaired processes of neuron regulation.

One of the aims of pathophisiology is to reveal laws and regularities of the development of diseases and morbid conditions.

- A disease makes biological and social capacity of a person more restricted.

While a disease is progressing one can see a decrease in the capacity of the organism failing to meet its biological and social needs, a decrease of its adaptability to the changed conditions.

A disease is a dynamic complex interrelated with pathogenic and adaptive reactions and processes, developing in the organism.

The mechanism of the development of any disease usually includes processes of two types: disturbance and adaptation of the organism to the changed conditions.

The balance of the processes of adaptation and damage with predominance of adaptive processes secures the survival of an organism when it is affected by a disease.

So in such conditions the physician has to stimulate adaptive processes to make the treatment successful.

The above-stated sentences list the most essential characteristics of the concept 'disease'.

Therefore, a **disease** can be defined as follows:

- A disturbance of normal life processes of the organism which occurs due to hereditary genetic factors and or due to the effect of external factors on the organism, characterized by the development of a dynamic complex of interrelated pathogenic and adaptive changes as well as by restricted biological and social capability of people.

MECHANISM OF ONSET, DEVELOPMENT AND OUTCOME OF A DISEASE

The mechanisms of onset, development and outcome of a disease are dynamic. They change in the course of their development. The development of a disease is determined by its cause, conditions oa development and the organism's reactivity and resistance. This accounts why one and the same disease develops differently in different patients.

A predisease (premorbid condition): The development of a disease mostly starts with a condition designated as a predisease (premorbid state. (A premorbid condition is neither a disease nor a healthy state). This is a state of relative insufficiency of adaptive processes when increased strain may provoke a disease onset.

In these conditions the influence of any agent (not pathogenic in other conditions) can cause a disease. A chronic stress is a good example of this condition. The condition of a predisease is not characterized by any specific symptoms. It can be revealed by means of load tests, or by means of functional tests which help to reveal decreased of the efficiency of the adaptive mechanism of the organism. This employs pharmacological tests, dosed physical loads and other functional tests.

Stages of a Disease.

1. The latent period or incubation period of an infectious disease. The incubation period of a disease lasts from some hours to some days or years. The patient must be isolated or hospitalized.

2. Prodromal period of a disease. The patient develops generalized clinical symptoms of a disease (complaints of a headache, slight malaise, chills, rheumatic pains in his joints as well as muscular pains). The doctor can make a preliminary diagnosis in this period of disease development.

3. Dromal period of a disease. It is marked by all clinical characteristics of a disease. In the dromal period the patient develops all specific clinical symptoms. The doctor has to make the final, basic diagnosis in this period of disease development.

4. Outcome of a disease will be favorable or unfavorable.

- recovery - complete or incomplete
- recurrence
- chronic disease –remission and exacerbation

Terminal state

- preagonal state
- agonal state
- clinical death
- biological death.

A clinical death is characterized by a number of symptoms. The patient is unconscious. The pulse in carotid and femoral arteries is not felt. Pupils are dilated. There is no reaction to light. It is necessary to perform urgent artificial respiration (external chest massage, cardiac defibrillation). Time of resuscitation is 10 min.

The basic method of pathological physiology is a pathophysiological experiment. It takes two stages: simulation of a pathological process and the study of its dynamics.

The role of experiment consists in observing a pathological process from its start to end. A physician cannot trace the disease development from its onset to its end.

The experiment allows a doctor to affect the organism of the animal using the methods which cannot be applied in hospital settings.

All experiments are divided into acute and chronic ones.

To study pathological processes the following basic experimental methods are used.

The first is the method of organ exclusion. This method consists in removing an organ surgically or in making it inactive using heat, cold, radiation or large doses of antibodies. This is effective in endocrinology. Thus, removal of the pancreas makes possible to establish a causal relationship between diabetes and the pancreas.

The second is the method of stimulation. For example, Valter stimulated the nervous sympathetic fibres and found that arteries can contract.

The third is the administration of drugs whose effect is well-known (hormones, enzymes, antigens, etc.).

The forth is the method of isolation of organs and culture of tissues.

This method was used to study the theory of anaphylaxis.

The fifth method is the method of comparative pathology.

The role of this method was demonstrated by Mechnickov. He proved that human pathological processes result from the reactions developing in the course of animal evolution.

A pathological experiment consists of four stages:

1. Preparation for questioning
2. Choosing a particular method
3. Planning the experiment.
4. Analysis of findings.

A pathological reaction is a reaction which is inadequate to the force, direction and duration of the acting stimulant.

A pathological process is a combination of pathological and adaptative reactions.

A pathological state is a long pathological process.

A disease involves both damaging and defense mechanisms which results in dramatic changes in the organism. All these have a negative effect on the vital and social activity of a person.

The Course of Pathology consists of three parts:

1. Nosology which originated from the Greek word "disease"
2. Typical pathological processes
3. Pathology of particular organs and systems.

A pathological process is a unity of pathological and defense reactions.

A pathological status is a permanently existing pathological process.

One of the most important and difficult questions is the problem of establishing the cause of a disease. The tactics of the physician and the success of treatment of various diseases depend on the correct solution of this problem. Pavlov believed that a problem of etiology is the least investigated problem of medicine. In the course of development of natural history the theory of etiology of diseases has been changing. Each etiological theory was influenced by the dominant ideas of the time it was formed at. The old theory could not account for

new facts. There were two ways of doing research: either to deny the facts or to change theories interpreting them.

The ancient medicine gave rise to the idea of a causative agent as a major etiological factor. XVII –XVIII centuries witnessed the development of a new doctrine known as mechanical determinism.

The mechanical determinism of XVII-XVIII centuries was of great significance for the development of the theory of pathology. Within a framework of mechanical determinism some basic methods of establishing causal connection (method of isolation, method of similarity, method of differences, method of attendant changes, method of remainder) were elaborated. These methods are still of great importance nowadays.

The important stage in the development of this scientific trend was elaboration of the theory of **mechanical monocausalism**.

The origin of this theory was prompted by discoveries of infectious pathology. Within a short period of time the causative agents of most widespread infectious diseases were discovered which was inspired by Paster's idea that diseases may be caused by infectious agents. Many scientists overestimated the importance of microbes in the development of diseases.

Monocausalism was most fully reflected in the **conception of Genle - Kock**:

1. A certain microbe causes a certain disease, it can be found neither in healthy people nor in people suffering from other diseases.
2. A microbe can be isolated in a pure culture.
3. Pure microbial culture will cause the disease whose causative agent it is supposed to be in experiment.

This conception was of great importance as it channeled the research into discovering numerous microbes.

However, there was some clinical evidence which contradicted this conception. Firstly, the study of severe epidemics revealed that not all people get infected and develop a disease. Nor all of those infected die. Secondly, there was experimental evidence that a hen which is not subject to anthrax in ordinary

conditions dies if its legs are kept in cold water for a while. Thirdly, milkmaids that had had cowpox did not catch smallpox during epidemics. Finally, in 1884 Lefler discovered the fact of carriage of bacilli. He found virulent streptococci and pneumococci on the mucous membranes of the pharynx and on the tonsils of healthy people.

Later a new theory of **conditionalism** gained popularity. The founder of that theory was Ferworn. He formulated five principles of this conception.

1. The first of them is as follows. There are no isolated and absolute things. All processes or states are conditioned by other processes or states.

2. There are no processes or states which are determined by a single factor. All processes or states are conditioned by a large number of factors (doctrine of multiple conditions).

3. Every process or state is unequivocally determined by the sum of their conditions

4.Every process or state is identical to the sum of their conditions.

5. All conditions of any process or state are equally significant.

Conditionalism is a subjective idealism theory. Microbes alone can not account for the origin of infectious processes. But we should not underestimate the role of microbes in this process.

Another step in the development of the doctrine of etiology is **constitutionalism**. The founders of this theory believed that diseases may be caused by a constitution type. These types are as follows: normal, asthenic or hyperstenic constitution. Each type of constitution has its own peculiarities. People of asthenic constitution are subject to stomach ulcer and tuberculosis. People of hyperstenic constitution are likely to suffer from myocardial infarction or bronchial cancer. This theory is based on the theses of formal genetics and on genotype invariability. However, a genotype can change under the influence of many exogenous and endogenous factors. Therefore, this theory can not be considered true.

The next theory was elaborated by **Zigmund Freud**. This author distinguished three main systems in the psychic (mental) structure of a person: the conscious, the subconscious and the unconscious. The latter is the home for sexual instincts. The conscious constantly suppresses these instincts. Freud believed that a daughter's love for her father, a son's love for his mother are manifestations of sexual instincts. Human consciousness constantly suppresses these sexual instincts. But having a high power charge they tend to struggle their way to consciousness. This results in the development of numerous diseases such as schizoprenia, epilepsy, neurosis, etc.

Zigmund Freud's conception had a great effect on the western medical science. It also gave rise to a new branch of medicine, i.e. **psychosomatic medicine**. The supporters of this branch of medical science suppose that diseases may be caused by psychological conflicts in childhood. Different pathological processes are conditioned by different stages of children's development when disorders occur.

Under 6 months of age an infant seeks for his mother's love and has a food instinct. Disorders at this age lead to bronchial asthma or ulcer. Under 3 years of age a child has an inclination for analysis. They often break their toys and other things. If parents forbid to do this a child gets aggressive and spasms of the muscular system occur. From 3 to 6 years a child develops a sense of self and sexual feelings. Disturbances at that age will result in hysteria and in various sexual disorders.

Thus, we have outlined the main theories of etiology in medicine. Nowadays etiology is a theory of causes and conditions of a disease development.

A cause determines specificity and quality of the bodily reaction to a pathological process. A cause also determines connections and regularities of the processes. For example, tuberculosis is caused by Micobacterium tuberculosisIt is responsible for specific and morphological changes typical of it.

The following these underlie the modern idea of causality:

1. All natural phenomena have their own cause, there are no causeless phenomena.

2. The cause is material, it is independent of our existence.

3. The cause interacts with the organism. Changing the body, the cause changes itself.

4. The cause gives a new quality to a process. It is the cause that makes a pathological process special and unique.

5. Classification of causes:

1. Exogenous: physical, chemical, biological, psychic/mental and social.

2. Endogenous.

Conditions.

1. Psychic/mental conditions in childhood.
2. Urbanisation.
3. Industrialisation.
4. War.
5. Unemployment.

PATHOGENESIS

Pathogenesis (from Greek: Pathos – suffering, genesis – origin) is a theory of the mechanisms of origin, development and outcomes of pathological process.

Pathogenesis can be divided into many stages or links which form a cause and effect relationship.

A cause and effect relationship means that exogenic influence is mediated through the internal basis of interaction. Effect is not a mirror reflection of exogenic influence but it is the result of interaction of exogenic and endogenic processes. This is a process in the course of the cerebral cortex and the reticular tissue of the brain stem are successively stimulated.

Categories of Pathogenesis

The Cause and Effect Relationships

Pathogenesis of a disease can be divided into several stages or types of connections and all these stages form a cause and effect relationship. A cause becomes an effect or vice versa. For example, the first stage in the pathogenesis of a traumatic shock is pain. A strong pain leads to the depression of vitally important centers, to a decrease of blood pressure, in particular. This is the cause of oxygen insufficiency. Hypoxia of the brain results in a depression of the motor center vessels and to the most dramatic decrease of blood pressure. As you can see changes of causes and effects lead to the formation of vicious circle. The significance of a vicious circle can be illustrated by windiness. Accumulation of air in the intestines hinders their motor and secretory functions that decreases fermentation, and lead to the formation of gases and increased windiness.

The cause and effect relationship in pathogenesis is of great practical interest. This enables the physician to make a purposeful intervention into the development of diseases. It is nessesary to take into account that not all the links of pathogenesis are equally important. Among them there are main and secondary ones. The main link of pathogenesis is the one without which no process can develop.

For example, in diabetes the main link of pathogenesis is deficiency of insulin. The administration of the hormone eliminates other manifestations of diseases such as hyperglycemia, coma. In acute pancreatitis the main link is the activation of proteolytic enzymes of the pancreas which damages the tissue of other organs. The most effective in this case is inhibition of proteases.

Local and Systemic in Pathogenesis

The study of pathogenesis of diseases proved that hare are neither purely local nor purely systemic diseases. The effectiveness of treatment depends on the correct understanding of this idea. All diseases are local and systemic at the same time, which determines the development of processes. Dental caries can be treated

using a stopper. If caries results from a systemic disorder of mineral and albumin exchange it requires a general treatment.

The correlation between local and systemic changes must be timely considered. A local process, for example, a furuncle can develop as a result of the impairment of defense mechanisms of the organism which limits this process and makes it local.

Structure and Functions

At the beginning of our century there was a heated discussion of Virchov's doctrine. The author of the theory of cell pathology believed that the more cells are damaged in the organism the more severe is the condition of a disease. However, facts which did not comply with this theory were revealed. The development of diseases was interpreted only on the basis of functional disorders associated with impaired neuroendocrine regulation but not involving the initial damage of the organs and tissues.

The question about functional and morphological changes of a disease turned out to be difficult enough. At that time this idea was of great importance for determining a disease treatment.

Electron microscopy significantly enlarged our knowledge of structure and functions of cells. It has been established that many diseases result from structural defects of macromolecules.

Nonspecific and Specific Signs

Every disease can have its signs that are typical of this disease only (for example, irradiation of the pain in angina pectoris), while other signs are typical of many diseases or even for all. This common nonspecific aspect of pathogenesis depends on the reactions of the organism developing in the course of evolution and is hereditary. There are five *nonspecific reactions*:

1) **Parabiosis.** This is stable, non-spreading excitation, which occurs in damaged excitable tissues. It is important in pathogenesis of some forms of cardiac blocade.

2) **Dominant reaction.** This is a condition of a stable rise of excitability of the group of nerve centres, which regulates the overall activities of the body. The dominating motivation gives rise to other dominants such as nutritional, sexual, etc.

3) **Neurogenic Dystrophy**

The cerebral cortex is connected with the inner organs. Damage of function of the cerebral cortex can cause pathological impulsaston. The nervous system is responsible for regulating the nerve supply of the organs and tissues ensuring their normal metabolism as well as differentiation of their cells.

The development of atrophy in peripheral paralyses and trophic skin ulcers in diabetes mellitus can illustrate a disturbed neurotrophic function. i

4) **Stress**

The theory of stress was created by Gans Selier. The scientist proved that different stimulants (warmth, cold, pain and others) always cause typical nonspecific reactions. In all cases synthesis of corticotrophin, a hormone secreted by hypophysis and stimulating production of adrenal hormones, increases. These hormones help the organism to adapt to stimulants.

A pathological reaction is a reaction inadequate to force, direction and length of stimulation.

A pathologocal process is a combination of pathological and defense reactions.

A pathological state is a permanently existing pathological process.

QUESTIONS FOR DISCUSSION

1. The subject and objectives of pathophysiology
2. The history of pathophysiology.
3. The structure of pathophysiology.
4. Interrelation of pathophysiology with other theoretical and clinical subjects.

5. A pathophysiological experiment.

6. The structure of a pathophysiological experiment and the tasks of each stage.

7. The conception of therapy according to etiology, pathogenesis and elimination of symptoms of a disease.

8. The conception of health, proceeding health and disease. Stages and outcomes of a disease.

9. The concept of pathological reactions, pathological processes and pathological state.

10. The subject of etiology.

11. Mechanical monocausalism in medicine.

12. The essence of criticism of conditionalism.

1.Constitutionalism in medicine.

2.The essence of Freudism.

3.Classification of etiological factors.

Subject of Pathological Physiology.

First Level Tests{Tests of the First Level}.

1. Pick out the basic method of pathological physiology.
   1- acute experiment;
   2- chronic experiment;
   3- experiment involving elaboration of pathogenic therapy principles;
   4- functional structural experiment;
   5- pathophysiological experiment;
   6- theoretical development of the basic stages of pathogenesis.

2. Name successive stages of a pathological experiment:
   1- Study of normal indices of body activities;
   2- reproduction of human diseases in animals;

3- study of abnormalities arising in the course of a pathological process development;
4- study of the original values of parameters corresponding to the objectives of the experiment;
5- experimental study of human diseases;
6- experimental trials of new drugs;
7- experimental therapy;
8- modeling of a pathological process.

3. The objective of the first stage of a pathological experiment is
1. to study physiological parameters of intact animals;
2. to study the original morphofunctional indices in experimental animals;
3. to study indices that can be designated as normal.

4. The objective of the second stage of a pathological experiment is
1. to model a pathological process;
2. to reproduce a human disease in experiment;
3. to study morphofunctional indices in a pathological experiment;
4. to develop a hypothesis of mechanisms of a pathological process development;
5. to study abnormalities;
6. Step-by-step reproduction of the whole chain of cause and effect relationship;
7. experimental testing of etiological concepts of a particular process.

5. The object of the third stage of a pathological experiment is:
1- to work out principles of pathological therapy;
2- to test a hypothesis and to develop a theory of pathogenesis;
3- to have a trial of new drugs, to evaluate their therapeutic value and possible harm (side effects).

4- to test the effectiveness of available medicinal agents and to elaborate the optimal scheme of treatment

6. What is the main idea of the notion «pathological process»?
   1- A set of damaging reactions;
   2- A set of defense and adaptive reactions to damage;
   3- development of cause and effect relationship in response to damage and defense reactions occurring the organism;
   4- dialectic unity of damaging and defense reactions of the body.

7. What is the main idea of the notion «disease»?
   1- Disease is a life of a damaged body involving compensatory processes;
   2- Disease is a number of deviations from the parameters of normal functioning of the body.
   3- Disease is impaired vital activity of the body affected by damaging agents.
   4- Disease is a dialectic unity of damage and physiological defense measures resulting in functional disturbances of different systems and their regulation.
   5- Disease reduces biological and social activity of an individual.

8. Pick out the examples of typical pathological processes:
   1- Iron deficiency anemia.
   2- Inflammation.
   3- Glomerulonephritis.
   4- Fever.
   5- Hypoxia.
   6- Pneumonia.

7- Hypertension.

8- Tumor.

9- Ulcer of the stomach.

10- Allergy.

11- Disturbances of peripheral circulation and microcirculation.

12- Toxic goiter.

9. Pick out the up-to-date definition of the notion «etiology».

1- Etiology is the study of a cause of a disease, which states the principle of a cause being equal to action.

2- Etiology is the study of causes and conditions of onset and development of diseases.

10. Which thesis of causative theory do you consider to be correct?

1- The effect of a particular damaging agent is an essential and sufficient cause of disease development.

2- A number of equivalent agents or conditions which caused a disease are of prior importance for the onset of a disease.

3- A specific cause of a disease acts on the body in particular conditions. These conditions are of great importance; they can either intensify the effect of the cause or counteract it.

11. Which definition of the notion «pathogenesis» do you consider to be correct?

1- Pathogenesis is a study of a disease origin;

2- Pathogenesis is a study of mechanisms of onset, development and outcome of a pathological process or disease.

3- Pathogenesis is a set of changes occurring in the body in the course of disease development.

12. Which links of pathogenesis are of crucial importance for the understanding of the mechanism of disease development?

1- A set of damaging reactions.

2- Establishing the main link of pathogenesis.

3- A set of defense and adaptive reactions.

4- Analysis of pathogenic stages linked by means of cause and effect relationships.

5- Vicious circle formation.

Second level tests

13. Give the definition for the notion "pathologic process".

14. What does the phrase "typical pathologic process" mean?

15. Give definition for the notion "disease".

16. Give definition for the notion "etiology".

17. Give definition for the notion "pathogenesis".

18. What does "the major phase of pathogenesis" mean?

19. What does the term "cause-and-effect relationships" mean?

20. Give the examples of the formation of cause-and-effect relationships in the course of disease development.

21. What does "vicious circle" mean?

22. Give the examples of "vicious circle" formation in the course of disease development.

FEVER

Fever is a typical pathological process, which occurs when pyrogens affect the thermoregulatory centre which is characterized by active temporary reorganization of thermoregulation aimed to increase the temperature of the internal medium of the organism regardless of environmental temperature.

Fever development is caused by shifting the fixed point of temperature homeostasis to a higher level under the influence of many pyrogenic substances. There are exogenous and endogenous, primary and secondary, infectious and non-infectious pyrogens, which give rise to infectious and non-infectious fever accordingly.

Exogenous pyrogens of infectious nature are high-molecular lipopolysaccharide complexes of endotoxins, which are components of the membranes of Gram-negative microbes and are released when bacterial cells are damaged. The main carrier of pyrogenic activity which pyrogens contain is A lipoid. A lipoid, a hydrophobic component, which is in the outer membrane of a bacterial cell, is a lipopolysaccharide (LPS) molecule showing little variability. It interacts with superficial CD-14 receptors, located on the microphages, macrophages and other antigen-representing cells, causing their activation and synthesis of the secondary endogenous pyrogens. Highly active exopyrogens almost can hardly have any toxic and antigenic properties as well as specific pyrogenic specificity. The toxic effect of lipopolysaccharide pyrogens in the organism manifests itself under the effect of doses, which are hundreds of thousands times as high as the minimal pyrogenic dose. Their toxic and pyrogenic properties are conditioned by various chemical groups. The body develops tolerance to exogenous pyrogens when it is recurrently affected by them. Besides LPS, pyrogenic properties are present in polysaccharides of a bacterial capsule (levan, dextran), as well as flagellin of flagellate organisms and peptides composed of dextro-rotatory amino acids. All these so-called T-independent bacterial antigens activate different clones of B lymphocytes and stimulate production of secondary endogenous pyrogens. Gram-positive bacteria and fungi, which don't

contain LPS, are the source of a small amount of exogenous pyrogens such as lipoteichoic acid and peptidoglycan. Thermolabile protein substances, obtained from enterotoxins and exotoxins, for example, Staphylococcus aureus, Streptococcus haemolyticus, Corynebacterium diphtheriae, causative agents of dysentery, tuberculosis, paratyphoid and other pathogenic agents, belong to exogenous infectious pyrogens. Pyrogenic activity of thermolabile protein pyrogens is much lower than that of lipopolysaccharide pyrogens. Viruses, ricketsiae and spirochaeta induce the development of fever regardless of the lack of exopyrogens – polysaccharides, lipopolysaccharides, exotoxins, endotoxins – in them. But, after they get into macrophages and interact with lymphocytes, they promote the synthesis of secondary endogen pyrogenic substances by these cells. In this regard, herpes virus and Epstein-Barr virus are especially active.

Non-infectious pyrogens induce the development of aseptic fever also after the activation of macrophageal and other mesenchymal cells and production of protein pyrogenic substances by them in the body. Endopyrogens are released by myeloid malignant cells of in case of acute myeloid leukaemia, by malignant cells in case of lymphogranulomatosis (Hodjkin's lymphoma), melanoma and other malignant masses. Endogen pyrogens form in case of immunoalergic or aseptic traumatic damage of tissues as well as in case of development of ischemic or hemorrhagic necrosis, etc. Hence, the stimulation of production of leukocyte pyrogens does not necessarily accompany infectious processes and it may be also associated with different forms of allergy. In case of allergic reactions antigen-antibody complexes binding to specific receptors on the cell membranes of phagocytes, activate genes responsible for the synthesis of the secondary endogen pyrogens.

Thus, the effect of primary infectious and non-infectious pyrogens is mediated by secondary endogen pyrogens forming in the body, the latter being the adequate stimulants of the hypothalamic thermoregulatory centre.

Endogenous pyrogens represent a heterogeneous group of biologically active substances embraced by the notion of cytokines: leukocyte pyrogen (LP) or

leukocyte-activating factor interleukin-1 (IL-1α, IL-1β), interleukin-6 (IL-6), IL-8, TNF or cachexin, FNO β or lymphotoxin, interferon (INF-β, INF-γ, INF-α), macrophageal inflammatory protein-1α, as well as less active cationic proteins and colonystimulating factors (KSF). They are synthesized in the focus of infectious, aseptic or immunoallergic inflammations by stimulatedgranulocytes, monocytes of blood and lymph, tissue macrophages, natural lymphocyte killers, B lymphocytes, microglial and macroglial cells, mesaglial elements, endotheliocytes, APUD-cells and mast cells as a result of interaction of exopyrogens with specific receptors of the listed elements, and also as a result of pino- and phagocytosis of exopyrogens or damaged cell tructures of the organism, immune complexes, etc. Endopyrogens may form in leukocytes under the influence of lymphokins and pyrogenic steroid hormones of etiochonalane type, a natural hepatic metabolite of androgens or progesterone analogues. In contrast to exogen pyrogens secondary endogen pyrogens don't cause the development of tolerance in case of their sunsequent formation in the organism.

For a comprehensive study of the mechanisms of fever development it is necessary to have an idea of the structural and functional organization of the thermoregulatory apparatus. One of the main functions of the thermoregulatory system is forming a fixed point of temperature homeostasis. A fixed temperature is a result of integrating the signals, passing from the cold and heat receptors of the skin and the inner organs to the specific thermosensitive neurons of the hermoregulatory centre and direct influence of a local temperature on them. They are located in the mesencephalic and bulbar reticular formation, olivary nucleus, hippocampus, septum, cerebral cortex and thermosensitive zone of the spinal cord. But most of them are situated in the preoptical zone of the anterior hypothalamus. The heat and cold sensitive neurons, forming a measuring unit ('thermostat'), receive direct humoral and reflexive temperature influences through the relevant receptors. The mediator of heat impulses is noradrenaline, and the mediators of cold receptors are serotonin and acetylcholine. The stated thermoneurons transmit impulsation about the nature of temperature influence to the 'etalon' interneuron

apparatus of comparison ('fixed point'), which is characterized by spontaneous impulse activity. They perceive information and form a fixed point of temperature homeostasis. Acetylcholine serves as a mediator in the neurons of the 'fixed point'. The signal of discoordination generated by intercalary neurons is transmitted by vegetative sympathetic, parasympathetic and somatic neurons, which make up the effector section of the thermoregulation centre. The mediators of efferent impulsation are noradrenaline and acetylcholine. The latter regulates the mechanism of heat emission, heat production and maintains the internal temperature of the organism in full accordance with the fixed point of temperature homeostasis. The signal of comparison, which arises in interneurons is necessary for proper feedback and stabilization of the function of thermosensitive neurons. It also maintains constant normal temperature and secures its return to a normal value after a decrease or an increase.

There are three stages in the development of fever: 1 – a rise of temperature; 2 – a fixed higher temperature; 3 – a decrease of temperature to the initial value.

The first stage of fever is characterized by limited heat emission and a subsequent increase of heat production. But there is no uniformity in determining the mechanisms of pyrogen action and the changes of thermoregulation processes at this stage of fever.

Some authors think that these mechanisms are as follows. Endopyrogens circulating in the blood penetrate through the hematoencephalic barrier (HEB) and exercise direct specific influence on thermosensitive neurons of the hypothalamic thermoregulatory centre. It is accompanied by the activation of the enzyme of phospholipase A_2 resulting in a release of arachidonic acid from phospholipids of the neuron membranes. Then the enzyme of cyclooxygenase (one of prostaglandin synthases) and the synthesis of PGI-2 are activated, these stimulate adenilate cyclase and cause an increase of 3,5-cAMP concentration increasing in the cytoplasm of these neurons. The metabolism of neurons acting as central thermosensors changes in the process of activation of AMP-dependent proteinkinases and protein phosphorilation. As a result of metabolic transformation

the excitability of cold sensitive neurons increases and of that of heat sensitive neurons decreases, and the internal temperature of the organism is perceived as low. Consequently, the mechanisms responsible for preservation of heat in the organism are activated.

According to the other data, endopyrogens cannot have a direct effect on the membranes of thermosensitive neurons of the measuring unit or the "etalon" intercalary neurons of the comparison section of the hypothalamus as they cannot penetrate through the HEB, which is impermeable for large hydrophobic polypeptide molecules. They penetrate not into the tissue of the hypothalamic parts of the brain proper but only into the vascular organ of terminal plate (VOTP), one of the so-called circumventricular organs, which is located 'beyond the barrier'. Endopyrogens intensifying the synthesis of cyclooxygenase in the cells of VOTP contribute to formation of arachidonic acid derivatives. It is especially important that endothelium of VOTP is highly sensitive to bacterial lipopolysaccharides and when the latter affect endotheliocytes of the highly permeable HEB area they can stimulate the production of PGI-1 and PGI-2 by the cells of the vascular intima without involving leucocytic pyrogens. Lipophilic liposoluble PGE easily penetrate both in heatsensitive and in 'etalon' interneurons of the fixed point of the thermoregulatory centre, and have a direct effect on neuron membranes, change metabolism patterns in cells as well as the degree of their excitability, thus providing fever development.

In spite of the fact that about 20 different metabolites are synthesized (called mediators of fever) in the anterior hypothalamus under the influence of different pyrogens, PG-1 and especially PG-2 which are secreted in the hypothalamus, mainly, under the effect of IL-1, IL-6 and TNF are considered to be of greatest significance in increasing the fixed point of temperature homeostasis by many scientists. Synthesized PGI form adenilatecyclase and inhibit phosphodiesterase, that assists the accumulation of 3,5-cAMP either in the thermosensitive neurons or in the 'etalon' neurons of the thermoregulatory centre. In conditions of accumulation of intracellular 3,5-cAMP, increaseв as well as reduced intracellular

concentration of Na^+ and decreased iron content in tissues of the hypothalamus as well as content of Ca^{2+} in neurons, their sensitivity to cold increases and sensitivity to direct heat and reflex influence decreases. In this case the pattern of the impulse activity of intercalary neurons of the comparison unit changes and the fixed point of temperature homeostasis rises. As a result, the thermoregulatory centre perceives the normal temperature of the blood and tissular fluid in hypothalamic area and the stream of the afferent impulsation from peripheral thermosensors as a signal of cooling, therefore, the mechanisms limiting heat emission and increasing heat production and the temperature of the internal medium of the organism are activated. When the excitability of thermostat' neurons and those in the 'fixed point' of the hypothalamic thermoregulation centre changes impulsation from cold and heat sensitive neurons is easily perceived by interneurons of the comparison unit and transmitted to the neurons of the effector section. The signal of discoordination generated by the neurons of the 'fixed point' causes the inhibition of parasympathetic neurons of the anterior hypothalamus which is the centre of heat emissions and simultaneous stimulation of sympathetic neurons of the posterior hypothalamus, i.e. heat production centre. It is accompanied by increased catecholamine synthesis, intensified heart activity and redistribution of vascular tonus: dilatation of the vessels of some inner organs and a neurogenic spasm of peripheral vessels resulting in the development of moderate secondary hypertension and polyuria. Constriction of the skin vessels leads to a decrease in their blood supply and heat emission by means of convention, irradiation and perspiration. In this case the skin becomes cool, pale and, sometimes, cyanotic as due to increased level of reduced hemoglobin in the blood. Piloerection which induces the development of the 'goose flesh' symptom occurs. In most patients the rate and depth of respiratory movements (and therefore, heat emission) are limited.

Thus, an increase of the internal temperature is primarily caused by considerable limitation of heat emission and accumulation of heat in the organism. An additional increase of thermal energy arises as a result of activation of the mechanisms of contractile and then non-contractile thermogenesis. When the rise

of body temperature is not sufficient and it does not correspond to the fixed point of temperature homeostasis a further increase of thermal energy in the organism is achieved by activation of contractile thermogenesis. The limited influx of warm blood to a number of inner organs and skin caused their cooling. A several degrees' decrease of skin temperature leads to the stimulation of cold sensitive receptors and the propagation of afferent impulses to the neurons of the brain stem reticular formation, thalamus, hypothalamus and sensitive zone of the cerebral cortex. As a result, a feeling of cooling arises and the corresponding behavioural reactions aiming at increasing heat production and decreasing heat emission. Due to stronger activation of cold sensitive neurons of the anterior hypothalamus and adrenergic neurons of the posterior hypothalamus the activating influence of the reticular formation on the neurons of the red nucleus of the mesencephalon as well as the nuclei of craniocerebral neurones, on spinal α-, β-, γ-motorneurons and later skeletal musculature intensifies. This influence is transmitted to skeletal muscles. It leads to the additional stimulation of sympatheticoadrenal system, secretion of catabolic hormones, stimulation of contractile and non-contractile thermogenesis by activating the spinal reflex feedback mechanism involving muscular spindles, increased thermoregulatory muscular tonus and development of muscular shivering. At the beginning asynchronic contractions of muscular fibres take place, which is perceived as tonic muscular strain. Further, muscular activation synchronizes contractile activity of separate motor units. Thus, muscular shivering arises: involuntary volley-like contractions of various muscle groups including masseters occur. It is expressed in teeth chattering. Contractile thermogenesis conditioned to some extent by the activation of thermosensitive neurons in the C5-Th1 segments of the spinal cord, is one of the main heat sources which is achieved by intensified muscular bioenergetics and increased body temperature to the level of a new fixed point of temperature homeostasis. Skin cooling and activated contractile thermogenesis are accompanied by arising subjective feeling of rigor.

The emergency contractile thermogenesis is followed by the action of delayed non-contractile thermogenesis conditioned by activation of the

mechanisms of chemical thermoregulation. In conditions of considerable activation of sympathetic influence the secretion of adrenaline by adrenal glands and the secretion of thyroxin by the thyroid gland increase. Besides, IL-1 stimulates the secretion of somatostatin, corticoliberin, corticotropin, glucocorticoids, thyroliberins and thyroid hormones and inhibits hypothalamic production of somatoliberin and insulin by the pancreas which weakens anabolism and intensifies catabolism. Non-contractile thermogenesis is conditioned by overall activation of metabolism under the influence of the mentioned hormones as well as glucagon and parathormone, especially in the liver, fatty tissue, brain and skeletal muscles, which are actively involved in the chemical thermogenesis as in the contractile one. Catecholamines intensify the synthesis of cAMP in the lipocytes of the white and brown fatty tissue, especially in children, and cause a relatively rapid increase of lipolysis. There is a large amount of mitochondria, cytochromes in the adipocytes of the brown fatty tissue. Most intensive oxidation without ATP accumulation, but with a primary heat increase is observed. It is conditioned by the fact that when acting on adipocyte receptors adrenalin activates the peptide thermogenin localized on the inner surface of lipocyte mitochondria, increases lipolysis and stimulates non-phosphorylating oxidation and thermogenesis. An increase of concentration of fatty acids in the blood and cells results in decreased coupling of respiration and phosphorylation and consequently, in increased share of primary dispersed heat, mainly, in the muscular tissue. Adrenalin activates glycogenolysis and aerobic glucose oxidation in the liver, but glucocorticoids conduce to gluconeogenesis and decay of new portions of endogenic glucose. Thyroid hormones increase the functional activity of K^+-Na^+-ATPase, which generates 30% of the heat value of the main metabolism. Besides, they conduce to mitochondrial oxidation, activating the NAD-dependent electron-transporting system of glycerophosphate dehydrogenase, and increase lipolysis. High concentrations of thyroid hormones and some bacterial toxins cause the swelling of mitochondria in cells of different tissues, the uncoupling of free respiration and oxidative phosphorylation which makes the accumulation of primary heat possible.

IL-1 and TNF conduce to catabolism stimulation and inhibit anabolism. For example, they decrease the activity of lipoprotein kinase, thereby blocking lipogenesis in the fatty tissue. All this leads to a further increase of chemical heat production and a rise in the internal temperature of the organism.

At the second stage of fever a gradual increase of heat emission in the organism accompanies increased heat production; therefore, these processes are counterbalanced. An increase of internal temperature of an organism causes activation of heat receptors of the heart, kidneys, veins, abdominal organs, heat sensitive neurons of the spinal cord and the anterior hypothalamus. At the same time it is accompanied by limited impulse activity of cold thermoneurons of the thermo-regulating centre, decreased activity of the adrenergic neurons of the posterior hypothalamus and sympathetic effects, activation of the parasympathetic neurons and cholinergic effects. All these lead to dilation of peripheral vessels, increased flow of the warm blood to the internal organs and the skin, an increase of its temperature, intensified perspiration and heat emission. Besides, TNF and IL-1 decrease the sensitivity of smooth muscles to catecholamins, which also leads to the dilatation of peripheral vessels and the occurence of heat sensation, increased heat emission and an insignificant decrease of arterial pressure. The listed endopyrogens when affecting the endothelium increase capillary permeability, transsudation and intensify the hypotensive effect and heat emission. The activity of the cold thermosensors of the skin and internal organs decreases as a result of warming of the skin and other tissues. The afferent impulsation flow into the thermoregulation centre to the cold thermoneurons of the anterior hypothalamus and to the adrenergic neurons of the posterior hypothalamus is limited which is accompanied by decreased sympathetic effects on the peripheral organs. This results in a gradual decrease of the activating effect upon the neurons of the mesencephalic and bulbar reticular formation, nuclei of the cranial nerves, spinal motor and vegetative sympathetic neurons. The activity of thermosensitive structures of the C5-Th1 segments of the spinal cord simultaneously decreases.

The described changes underlie a decrease of contractile and non-contractile thermogenesis. Besides, muscular shivering as the main source of thermal energy usually disappears as soon as the internal temperature reaches about 39.5-40.0°C. Increased heat emission coupled with limited growth of heat production hinders a further rise of body temperature and makes it reach a higher level value. Besides, the body temperature rise is regulated by the system of endogenous antipyresis, which is activated under the influence of TNF. It includes the hypothalamic arginine-vasopressin (AVP) neuromodular mechanism of hyperpyrexia prevention by decreasing the excitability of the cold-sensitive neurons of the preoptical zone of the anterior hypothalamus and by decreasing the effects of sympathetoadrenal activity on the peripherals. The similar effect arises under the influence of thyroliberin, an intestinal inhibiting polypeptide, neurotensin and bombesin. Bombesin which is the most active of them increases the sensitivity of heat thermoneurons of the "measuring unit" in the hypothalamus, which prevents the origin of hyperpyrexia. At the same time TNF stimulates the production of α-melanotropin (α-melanocyte-stimulating hormone, α-MSH) and oxytocinin the hypothalamus. These oligopeptides affect the thermoregulation centres gradually limiting the body temperature rise without penetrating into the blood. Besides, increased production of natural antipyretics under the effect of IL-1 such as corticoliberin, corticotropin and hydrocortisone results in inhibited release of IL-1, IL-6 and TNF-α by the peripheral cells of the immune system as well as in the stabilization of cellular membranes involving reduced release of the arachidonic acid metabolites in the central nervous system which is based on the feedback principle. Lipocortin, which is believed to be a mediator of the glucocorticoid function, also inhibits the pyrogenic effects of IL-1 and IF. Somatostatin and the endogenic agonists of the opiate and barbituric receptors – endorphines and enkephalins, being also the natural antagonists of endogenic pyrogens, prevent hyperpyrexia development. Its development is hindered by the glycoprotein with a mass of 18 kD, a competitive blocker of cellular receptors for IL-1, uromodulin (Tamm-Horsfall protein, THP), high-affinely binding IL-1, cytokines, blockers of

the IL-10 cascade and transforming growth β-factor, soluble serum antagonists of the IL-1 and IL-6 molecules as well as TNF receptors. When the secretion of hormones by the hypothalamus, hypophysis, adrenal glands, thyroid and parathyroid glands is slightly inhibited, the process of chemical heat production slackens. Thus, the systemic reaction, the reaction of the acute inflammation phase and the internal temperature rise are self-limited at fever. The brain cortex produces the modulating, mainly, inhibiting effect on the state of the hypothalamic thermoregulation centre.

The third stage of fever is characterized by the considerable predominance of heat emission over heat production and return of the body temperature to the initial level. The latter is conditioned by decreased concentration of pyrogens in the body, gradual restoration of the sensitivity of the hypothalamic centre neurons to cold and heat direct and reflectory stimuli. As the sensitivity of the interneurons of the comparison unit normalizes, the fixed point of temperature homeostasis returns to its primary value. This is accompanied by more expressed inhibition of activity of adrenergic neurons, decrease of sympathetic effects and increase of activity of parasympathetic neurons of the effector section of the thermoregulation centre and cholinergic effects. As a result, further dilatation of the peripheral vessels, increased blood supply of the skin, intensified activity of the sweat glands and more excessive perspiration are marked. Simultaneously, a local increase of bradykinin production and a secondary stable increase of the lumen of cutaneous vessels, their filling with blood as well as heat emission occur. Perspiration is stimulated and diuresis increases. Metabolic processes which are still active enough are restored, heat production decreases and the body temperature gradually becomes normal. At this time patient's behaviour also causes heat losses. A temperature increase is not a mere consequence of exhaustion of pyrogen resources but it is an active reaction regulated as stated above, by numerous natural endogenous antipyretics. It is necessary not only to stop the action of the etiological factor, but also to make an active signal to terminate the program in progress. Particularly, the reverse impulsation flow from the neurons of the

measuring unit stabilizing the function of the thermosensitive neurons of the measuring unit of the thermoregulating centre and helps to fix temperature at the initial level. The restoration of the impulse activity of peripheral thermosensors located in different blood-warmed organs and tissues, also results in normalization of body temperature. However, it should be noted that an excessively quick decrease of the concentration of pyrogens in the blood and the termination of their action on the hypothalamic thermoregulating centre may be accompanied by a dramatic reduction (for 1-2 hours) of body temperature. In this period the predominance of the tonus of the parasympathetic nervous system over the sympathetic one exerts negative bathmotropic, dromotropic, inotropic and chronotropic effects on the heart. The latter results in lower cardiac activity, sharp dilatation of peripheral vessels, lower arterial pressure and impaired central hemodynamics. Therefore, a dramatic decrease of the body temperature is associated with developing acute vascular insufficiency or circulatory collapse which commonly occurs in children. According to the clinical signs the stages of fever are designated as chill, fever and sweat.

As any other typical pathological processes fever is often a defensive and adaptive mechanism, but in certain conditions it may be pathogenic. In case of some infectious diseases a rise of body temperature prevents multiplication of a number of pathogenic microbes, decreases their resistance to drugs. To some extent it is conditioned by development of hypoferremia and decreased zinc content which are necessary for multiplication and growth of bacterial agents in patients' blood. Metabolism, cytophagous ability of various cellular elements, antibody production, synthesis of properdin, interferons, interleukins and the activity of the hypothalamo-hypophyso-adrenal system are stimulated at fever; the secretion of adaptation hormones as well as barrier and antitoxic functions of the liver intensifies, immunobiological protection of the body in general is activated.

However, hyperpyrexial fever is characterized by the predominance of damage and disadaptation reactions. So, if the organism is susceptible to high temperatures, loss of consciousness, convulsive syndrome, marked tachycardia,

hypertonia and hypertension may occur. When fevers are recurrent or continuous iron deficiency anemia, muscular dystrophy or emaciation of the body occur. At the same time as oxygen consumption by tissues increases, ketosis and arrhythmia may develop. Cardiac insufficiency may also develop due to increased myocardium load due to volume and resistance. TNF and IL-1 stimulate the production of coagulants, thromboxan A_2 and leukotrienes E_4, by the endothelium as well as the development of disseminated intravascular coagulation (DIC) syndrome, increase the production of platelet-activating factor (PAF), NO and myocardiac depressor peptide. The latter is produced in the pancreas and APUD cells of the atria; it causes vasoconstriction in the internal organs, a decrease of the myocardium contractility and cardiac insufficiency. Particularly, the above-stated factors contribute to hypotension development, cardiac output decrease and systemic microcirculatory disturbances conditioning polyorgan insufficiency at sepsis caused by Gram-negative and Gram-positive bacteria. Pyrogenic cytokines may cause some systemic and local clinical manifestations in patients with AIDS, serious spirochaete infections, meningitis, arthritis, respiratory distress syndrome in adults and mycobacterial infections. TNF-α (cachexin) is anorexigen, as it inhibits the activity of the hypothalamic hunger centre and stimulates the functional state of the satiation centre. Emaciation of the body arising as a result of chronic infections, granulomatous processes, tumours (leucoses) is conditioned to a certain extent by high production of TNF. When TNF and IL-1 act together, they block membranous digestion and intestinal peristalsis, stimulate vomiting and diarrhea, destruction of the hepatocytes, hypercalcemia and acidosis; they may have a cytopathogenic effect and even cause a lethal outcome.

When the fever is continuous, local immunity of the oral cavity decreases because of developing hyposalivation, leading to the accumulation of oral microflora causing stomatitides and quinsy. In these conditions formation of dental deposit which contains a large amount of lipopolysaccharides (LPS) intensifies. Because of LPS the dental deposit activates local macrophages, granulocytes and

lymphocytes, whose products damage teeth and gums, thus giving rise to caries, periodontitis and other inflammatory processes in the oral cavity tissues.

As for neonates, fever usually develops in them in 3 months after their birth. Their body temperature slowly rises but, as a rule, it is not maintained at a high level, especially when the environmental temperature fluctuates. A dramatic rise of temperature is accompanied by neither a chill nor muscle shivering. The main heat source for them is metabolism activation and lipolysis in the brown fatty tissue. Brown fat is located in the interscapular area, behind the breastbone in the mediastinum, along the aorta, large vessels, spinal column and sympathetic trunk, in the axillary region, abdominal cavity, around the kidneys, adrenals and in sucking pads in the baby's cheeks. The brown colour of this fat is conditioned by numerous capillaries and mitochondria with their pigmented cytochromes containing ferrum. Brown fat is the most important heat source in the organism. The mitochondria of the brown adipocytes contain the protein of hermogenin which is the activator of non-phosphorylating oxidation. The brown fat cells are supplied with a large amount of noradrenergic receptors and sympathetic noradrenergic nerve endings. There are the paraortal ganglions along the spinal column in the neonatal brown fat. These are masses of chromaffin tissue producing noradrenalin. Noradrenalin prevails in the incretion of the adrenal medulla in the first 3-4 months of life. The activation of the sympathetic effects of adrenal chromaffin tissue and Zuckerkandle's organs in the neurogenic and humoral ways stimulates volley-like lipolysis and thermogenesis in brown lipocytes. The warming of blood in large vessels and the systemic effect of free fatty acids contribute to a temperature rise. Besides, the warmed blood flows out from the masses of juxtaspinal brown fat through the neonatal unique venous anastomoses into the cerebrospinal venous sinus and warms up the spinal thermosensors in the C5-Th1 segments. As a result, shivering thermogenesis is inhibited as a result, but tonic muscle activity is maintained. Therefore, contractile thermogenesis is practically of no importance for the mechanisms of body temperature rise in neonates having fever.

The facts that the regulatory centre of the neurogenic vascular tone as well as the thermosensitive receptor apparatus is functionally deficient and the hypothalamic neurons have low susceptibility to pyrogens in children since the moment of their birth also accounts for the peculiarities of fever development in newborns. Besides, unstabile metabolism, insufficient perspiration, poorly-developed skeletal muscles and heat-insulating properties of the skin, and subcutaneous tissue, as well as high specific body temperature are marked. This manifests itself as deficient chemical and especially physical thermoregulation. When the physical thermoregulation is deficient, no noticeable heat emission occurs, therefore, fever may have no manifestations in most children during the first year of life. However, in patients with serious infectious diseases a temperature rise is often marked. In these cases a temperature rise is conditioned by increased heat production, mainly, because of the effect of toxicants causing uncoupling of free respiration and oxidative phosphorylation in cellular elements of various tissues. At an early age, fever may be complicated with heat exchange disturbances and hyperthermia. In children above 1 year of age fever develops in the same way as in adults in uncomplicated cases and may play both a positive and often a negative role. Besides, systemic and local metabolic disorders, their clinical signs may be caused by the pathogenic effect of pyrogenic cytokines.

Thus, being the effector mechanism for mobilizing the immune system resources and metabolism to protect the organism against aggression fever, as well as other pathological processes is imperfect, therefore the problem of pros and cons of fever and of choosing the necessary antipyretic therapy has to be solved by a doctor in each particular case.

QUESTIONS FOR DISCUSSION

1Thermoregulation mechanisms. Main types of thermoregulatory disturbances.

2. Fever. Main differences between fever and overheating.

3. Pyrogens, their types and properties.

4. The role of primary and secondary pyrogens in fever pathogenesis. The role of interleukins.

5. Fever stages. Correlation of heat production and heat emission at different stages of fever development.

6. Disturbance of the functional state of the main life supporting systems of an organism during fever.

7. Changes of reactivity and resistance at fever.

8. Biological significance of fever.

9. Application of fever mechanisms in medical practice.

Tests of the First Level

1. Name exogenous etiological factors of fever.

1. Bacteria.
2. Viruses.
3. Mechanical factors.
4. Radiation.
5. Helminthes.
6. Immunological conflict.
7. Chemical factors.
8. Protozoa.
9. Fungi.
10. Thermal factors.

2. Name the sources of endogenous pyrogens.

1. Neutrophils.
2. Lymphocytes.
3. Monocytes, macrophages.
4. Cells of the vessel endothelium.
5. Cells of the skin epithelium and mucosal membranes.
6. Osteocytes.
7. Neurons of the brain.

3. What is the mechanism of chill/ague at the first stage of fever?

1. Loss of heat due to dilatation of vessels involving reactions of cold receptors.
2. A decrease of heat production.
3. A simultaneous decrease of heat production and heat emission.

4. Which mechanisms of thermoregulation are responsible for the maintenance of high temperature at the second stage of fever?

1. Termination of heat production increase.
2. A gradual increase of heat emission.
3. Relative equilibrium between heat production and increased heat emission.
4. All mechanisms

5. What thermoregulatory mechanisms dominate in time of a rapid decrease of body temperature at the third stage of fever?

1. A quick decrease of metabolic processes underlying heat production.
2. Poor synthesis and secretion of pyrogenous hormones.
3. Increased heat emission mainly due to hidrosis.
4. Combination of all these mechanisms.

6. Indicate neuromediators of thermosensitive region of the thermoregulatory center.

1. Acetylcholine
2. Noradrenalin
3. GABA
4. Histamine
5. Serotonin

7. Which is the terminal value of a body temperature rise when positive effects of fever are marked?

1. 0,5-1^{0}C higher than the normal temperature
2. 2-3^{0}C higher than the normal temperature
3. 4^{0}C higher than the ormal temperature

8. Pick out neuromediators of the thermodetermining area of the thermoregulatory center.

1. Acetylcholine
2. Noradrenalin
3. GABA
4. Histamine
5. Serotonin

Tests of the second level.

9. What is the main difference between the shifts of the thermoregulatory mechanisms during fever and overheating?

10. Give the definition of "fever"

11. What is chemical composition of exopyrogens?

12. Enumerate the main sources of endopyrogens.

1.
2.
3.

13. Name the stages of fever, supply the Latin terms for them.

1.
2.
3.

14. Indicate the direction of thermoregulatory processes at different stages of fever.

1. At the stage of a temperature rise– heat emission N, ↓, ↑, heat production – N, ↑, ↓,

2. At the stage of high temperature - heat emission N, ↑,↓, heat production N, ↑, ↓.

3. At the stage of a temperature decrease - heat emission N, ↑, ↓, heat production N, ↑,↓.

15. Complete and specify the elements of a pathogenic chain in the following scheme of fever pathogenesis (choose or add the correct items)

Microorganims → exopyrogens → blood cells → _____ → thermoregulatory center → activation of enzyme _____ → synthesis of _____ → "fixed point of thermogenesis" perceives blood temperature as increased (decreased) → changes of thermoregulatory mechanisms.

_____

↓ ↓

increased (decreased) of synthesis and secretion of hormones: _____, probable occurrence of _____ in the muscles of _____

vessels _____

↓

heat emission ↑,↓

↓

heat production ↑ ↓

↓

_____

body temperature ↑ ↓

16. List the effects of catecholamines which are involved by the mechanisms of temperature rise during fever.

1.
2.
3.
4.
5.

17. Name the effects of thyroid hormones which are involved by the mechanisms of temperature rise during fever.

1.
2.
3.

18. Name the main systems of the organism changing its condition during fever

1.
2.
3.
4.
5.
6.
7.
8.

19. Name the main functional disturbances of the nervous system during fever:

1.
2.
3.

20. Name the main functional disturbances of the endocrine system during fever:

1.
2.
3.
4.

21. Name the main functional disturbances of the cardiovascular system during fever:

1.
2.
3.

22. Name the main disturbances of the respiratory system during fever:

1.
2.
3.

23. Name the main changes in blood during fever:

1.
2.
3.
4.
5.

24. Indicate the main changes of the gastrointestinal tract:

1.
2.
3.

25. Name the general tendencies of diuresis changes at different stages of fever:

1.
2.

26. Name the main direction of metabolic changes during fever:

1.
2.
3.

27. What processes lead to a decrease of body weight during fever:

1.
2.
3.

28. Name the positive effects of fever:

1.
2.
3.

29. What are the negative consequences of fever?

30. What are general principles of fever treatment:

1.
2.
3.

LITERATURE.

1. Ado A.D. "Pathological Physiology M., 2000. – 518 p.
2. Ovsianikov V. G. "General pathology".Rostov, 1997. Part 1
3. Litvitski P.F. "Pathological Physiology". Part 1 M., 2003. - 807 p.
4. Zaiko N.N. "Pathological Physiology" .Kiev, 1996. – 550 p.
5. Vinay Kumar, Ramzi S. Cotran, Stanley L. Robbins "Basic Pathology" USA, 1997 .- 775p.
6. Ovsianikov V. G. , Eremina S. A. "General pathology"(pathological physiology). Questions & answes. Part 1. Rostov, 1999. – 200 p.
7. Arthur S. Schneider, Philip A. Szanto "Pathology" Board Review Series. USA. 1997. –399 p.

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Part 1.

(manual for third year students of medical colleges of higher education)

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