

Министерство здравоохранения республики Беларусь  
Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
Обсуждено на заседании кафедры  
Протокол №7 от 30.08.2017

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

Тема: **Инфекционный процесс. Лихорадка**

Theme: **Infectious process. Fever**

Время 3 ак. часа

**Actuality of the theme.** In all hospitals it is obligatory is carried out patients' thermometria. In the case history there is a temperature list where is the morning and evening temperature, as well as the diagram of its changes. According to type of the curve they define the fever type. It has diagnostical significance because a lot of infectious diseases are accompanied with fever with typical temperature curve. Fever has mainly protective role. Only in the persons with serious disorders of cardiovascular, nervous and other systems and in children the high temperature (above 39 °C) can be dangerous. The doctor must evaluate the fever significance in the patient and will plan the treatment.

**Learning goals of the lesson:** to study causes, mechanisms of development and significance of fever.

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

**Objectives of the lesson:**

1. To study classification, origin, mechanisms of action and main effects of pyrogens.
2. To study causes of onset, mechanisms of development and main manifestations of febrile reaction.
3. To be able to construct graphs of classical types of temperature curves for fever.
4. Be able to distinguish fever from other types of hyperthermia.

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

1. Mechanisms regulation of body temperature (normal physiology discipline)

**Control questions of the lesson:**

1. Infectious process: types, stages, general etiology and pathogenesis, its outcomes and complications, ways of prevention and principles of therapy.
2. Sepsis: etiology and pathogenesis.
3. Fever: definition, etiology, types, stages and pathogenesis.
4. Biological significance of febrile reaction for a body.
5. Temperature curves, their diagnostic value.
6. Change in metabolism and physiological functions in fever.
7. Pathophysiological principles of antipyretic therapy. Pyrotherapy.
8. Difference of fever from exogenous overheating and other types of hyperthermia.

**Calculation of study time**

Total study time 3 ac.hours

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

## Additional materials

### Infectious process

**Primary infection** – initial infection with organism in host.

**Reinfection** – subsequent infection by same organism in a host (after recovery).

**Superinfection** – infection by same organism in a host before recovery.

**Secondary infection** – when in a host whose resistance is lowered by preexisting infectious disease, a new organism may set up in infection.

It is a typical pathologic process lying in the background of infectious diseases; an orderly developing host of reactions (biochemical, immune, structural and functional) in the body in response to damaging effects of pathogenic microorganisms. Infectious process has developed during evolution as a form of interaction between the host and infectious agent.

Three stages of infectious process:

1. Entry and colonization of the host.

2. Invasion and growth in host tissues; elaboration of toxic substances.

3. The host response.

The host defence mechanisms against the entry of infectious agent:

- mechanical barriers:
  - epithelium of the skin
  - the flow of secretions from glands
- chemical barriers:
  - acidic environment of the stomach and urinary bladder
- normal microflora
- organism-specific immune system:
  - specialized macrophages and lymphocytes
  - surface immunoglobulins
- neurologic mechanisms:
  - gagging
  - coughing
- behavioral mechanisms

**Table 1 - Classes of Human Pathogens and Their Lifestyles** (Vinay Kumar [et al.], 2004)

Taxonomic	Size	Site of Propagation	Examples	Disease
Prions	30–50 kD	Intracellular	Prion protein	Creutzfeld-Jacob disease
Viruses	20–300 nm	Obligate intracellular	Poliovirus	Poliomyelitis
Bacteria	0.2–15 µm	Obligate intracellular	<i>Chlamydia trachomatis</i>	Trachoma, urethritis
		Extracellular	<i>Streptococcus pneumoniae</i>	Pneumonia
		Facultative intracellular	<i>Mycobacterium tuberculosis</i>	Tuberculosis
Fungi	2–200 µm	Extracellular	<i>Candida albicans</i>	Thrush
		Facultative intracellular	<i>Histoplasma capsulatum</i>	Histoplasmosis
Protozoa	1–50 µm	Extracellular	<i>Trypanosoma gambiense</i>	Sleeping sickness
		Facultative intracellular	<i>Trypanosoma cruzi</i>	Chagas disease
		Obligate intracellular	<i>Leishmania donovani</i>	Kala-azar
Helminths	3 mm–10	Extracellular	<i>Wuchereria bancrofti</i>	Filariasis

Taxonomic	Size	Site of Propagation	Examples	Disease
	m	Intracellular	<i>Trichinella spiralis</i>	Trichinosis

The main transmissions are:

- **direct contact** (including intimate sexual contact), e.g. soft tissue infections, gonorrhoea, genital herpes
- **inhalation**/droplet infection, e.g. common cold, pneumonia
- **ingestion/faecal–oral** route, e.g. gastroenteritis
- **inoculation or trauma**, e.g. tetanus, malaria
- **transplacentally**, e.g. congenital toxoplasmosis.

Infectious agents establish infection and damage tissues by three mechanisms:

- they can contact or enter host cells and directly cause cell death;
- they may release toxins that kill cells at a distance, release enzymes that degrade tissue components, or damage blood vessels and cause ischemic necrosis;
- they can induce host immune responses that, though directed against the invader, cause additional tissue damage.

Infectious diseases may be localized or generalized. Localized infections may be superficial or deep-seated.

Circulation of bacteria in the blood is known as bacteremia (viruses – viremia).

**Sepsis** is nonspecific infectious disease characterized by pathological systemic (generalized) homotypic reaction to the infection (with a wide variety of pathogens) and in the progression, leading to dysfunction of vital organs and systems

**Sepsis** does not arise on its own. It stems from another medical condition, such as an infection in the lungs, urinary tract, skin, abdomen (eg, appendicitis) or other part of the body. Invasive medical procedures like the insertion of a vascular catheter can introduce bacteria into the bloodstream and bring on the condition

Concept of sepsis based on four separate characteristics designated by the acronym PIRO. P stands for the predisposition, indicating pre-existing co-morbid conditions that would reduce survival. I is infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. R represents the response to the infectious challenge, including the development of SIRS. The last letter O stands for organ dysfunction and includes organ failure as well as the failure of a system such as the coagulation system.

**By clinical course sepsis :**

- Fulminant (symptoms appear at 12-24 hours, septic shock develops at 1-2-th day, duration about 5-7 days; the outcome is usually unfavourable)
- Acute (40%, symptoms manifest for several day, duration of 2-4 weeks, high mortality rate)
- Subacute (duration of 6-12 weeks, outcome is usually favorable)
- Chronic (develops, if not eliminate acute, duration - years with relapse and remissions)

**According to source of generalization sepsis are classified into:**

- traumatic (trauma and burn)
- postoperative
- inflammation (abscess, phlegmon)
- sepsis in internal diseases (pneumonia, etc.)
- angiogenic (for invasive procedures on the heart and blood vessels)
- abdominal (in complicated surgical diseases of abdominal cavity and retroperitoneal space)

**Pathogenesis**

Stimulation of Le by microbial toxins → massive release of cytokines → endothelial damage, serious microcirculatory, rheological, hemodynamic changes → violation of perfusion of vital organs → damage to vital organs → violations of perfusion → reducing resistance of various tissues to invasion of microorganisms → adhesion of circulating bacteria in their tropic tissues with the formation of secondary septic foci.

Without treatment, the disease progression is inevitable

Sepsis with signs of SIRS → severe sepsis with MODS and / or septic shock → progresses of organ dysfunction

### **Systemic Inflammatory Response Syndrome**

**SIRS** is a nonspecific generalized reaction of the body in response to a serious injury, infectious process or other stress reaction

#### **Criteria for SIRS:**

Two or more of the following are required:

- 1) Body temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$
- 2) Heart rate  $>90$  beats per minute
- 3) Respiratory rate  $>20$  breaths per minute or arterial  $\text{CO}_2$  tension less than 32 mm Hg or a need for mechanical ventilation
- 4) White blood count greater than  $12 \times 10^9/\text{l}$  or  $<4 \times 10^9/\text{l}$  or  $>10\%$  immature forms

### **Multiple organ dysfunction syndrome (MODS)**

It is a dysfunction of vital organs, in which independent maintenance homeostasis (without medical correction) is **impossible**.

#### **Signs of MODS**

- **CVS:** SBP  $<90$  mm Hg or mean arterial pressure  $<70$  mm Hg, continuing for at least 60 minutes in hypovolemia correction.
- **Respiratory system:** necessity oxygen therapy or a artificial lung ventilation to maintain  $\text{PaO}_2 > 60$  mm Hg; or a signs of acute respiratory distress syndrome on X-ray
- **Urinary system:** diuresis  $<0.5$  ml/kg per hour (for 60 minutes in hypovolemia correction), or a increasing creatinine in 2 and more times higher norm
- **Liver:** bilirubin concentration in plasma  $>20$  mmol/l within 48 hours, or a increase of transaminases twice norm
- **Gastrointestinal tract:** dynamic intestinal obstruction refractory to treatment, continuing for more than 8 hours.
- **Hemostatic system:** increase fibrinolytic activity on 18% and more; Tr decrease on 50% for 72 hours
- **Metabolic dysfunction:** pH  $<7.3$ , base deficit more 5, increasing the concentration of lactate in plasma in 1.5 times
- **CNS:** stupor

## **FEVER**

**Fever** is etiologic nonspecific and pathogenic the uniform of typical pathological process, described dynamic reorganization of function of thermotax system in reply to action of pyrogenic substances and shown rise in temperature of the internal environment at the supreme homotherm animals and the person.

**Fever** is a typical pathological process, which is characterized by reorganization of thermoregulation and  $\uparrow$  body  $t^{\circ}$  in response to pyrogens

The fever concerns to late enough purchases of evolution. Development of a fever in phylogeny is connected with a level of organization higher nervous system and formation of thermotaxic mechanisms. Therefore the fever is inherent only in the supreme homotherm animals and the person. Ability to be in a fever for the first time has appeared at rodents and insectivorous. At homotherm organisms sensitivity to pyrogenic substances depends on a level of their development (expressiveness of a fever increases in a line: the mouse - a rat - the rabbit - primates - the person).

During evolutionary development the fever was generated as nonspecific protective reaction of an organism in reply to occurrence in its internal environment of an alien material. Fastening of a fever in phylogeny is the proof of its protectively-adaptive value. However, as any typical pathological process, the fever can render pathogenic influence on an organism. Still P.N.Vesvolkin spoke, that “ a fever as genetically determined stereotype cannot be accomplished{perfect;absolute} ”. Therefore in each concrete case the fever demands flexible medical tactics and an individual approach which is defined{determined} by character of illness, age, features of disease and a beside of other factors.

## **Etiology of fevers**

The reason of a fever are pyrogens (from Greek. pyros - fire, pyretos - heat).

Classification of pyrogens

Pyrogenic substances can be divided on two big groups:

- Primary
- Secondary

Primary (exogenous) pyrogens can be the infectious and not infectious nature.

To infectious primary пироген concern: viruses, mushrooms, bacteria, rickettsia, одно- and multicellular parasites.

To not infectious primary pyrogens concern: proteins and proteincontent substances, lipids and fat-containing substances, steroids, nucleoproteids. The greatest pyrogeny possess lipopolysaccharids (endotoxin).

## **Properties of exopyrogens**

1. do not cause a fever independily.
2. temperature-stable.
3. Are nontoxic.
4. Not allergenic.
5. Not antigenic.
6. Are hapten.
7. To them tolerance develops at repeated application.
8. Cause a number of protective effects.
9. There is no group specificity.

Primary pyrogens do not cause a fever independily. Primary pyrogens cause a fever mediatly, promoting formation in a macroorganism secondary pyrogens. Secondary (leukocytic) pyrogens, formed in an organism, cause development of a fever. Primary pyrogens are etiologic factors, and secondary - pathogenetic.

Secondary (endogenous) pyrogens are produced in a macroorganism as a result of influence of primary pyrogens. They are formed mainly in phagocytic leukocytes (neutrophills, monocytes, macrophages), in lymphocytes - in a small amount. True pyrogens they are named in case of their ability to cause a fever.

Endogenous pyrogens are Interleukin 1 (IL-1), interleukin 8 (IL-8), interleukin 6 (IL-6), tumor necrosis factor - TNF, gamma-interferon (gamma-IFN).

## **Properties of endopyrogens**

1. Cause development of a fever.
2. Are developed {produced}, basically, in micro- and macrophages of an organism.
3. Are not toxic.
4. temperature label.
5. Do not possess specific specificity.
6. To them tolerance is not formed.
7. Raise {Increase} protective properties of an organism.
  - Strengthen phagocytosis.
  - Strengthen development of glucocorticoids.
  - Strengthen regeneration of tissues.
  - Strengthen detoxicative function of a liver.
  - Improve processes of microcirculation.
  - Secretion of endogenous pyrogens does not bring to ruin phagocytes.

It is necessary to note, that secondary pyrogens except for pyrogenic activity possess a number of specialized functions.

The Certain value in etiology of fevers have conditions at which the causal factor is realized. It is known, that conditions in itself cannot cause diseases, but are capable to affect on the etiologic agent.

Among conditions the important role is played with a condition of reactance of an organism, timeliness and adequacy of spent antibacterial therapy, etc.

### **The factors determining becoming of feverish process (On A.D.Ado, 1994г.)**

1. Condition of reactance (excitability) of the temperature thermal centers and peripheral thermoreceptors.
2. Activity of synthesis and transport mediators of fevers (acetylcholine, serotonin, peptides, etc.)
3. Changes of quantity {amount} and structure of leukocytes in blood of the patient during disease.
4. Speed of formation and allocation of endopyrogenes.
5. Permeability of blood-brain and histohaematic barriers.
6. Specific immunologic and allergic stage of an organism of the patient, caused by a condition immunocompetent systems, including development of antibodies, activity of lymphocytes and macrophages.
7. Nonspecific reactance of endocrine and immunocompetent systems.

Besides the degree of rise in temperature at various diseases depends on introduction raising of higher nervous system substances: caffeine, phenamin, etc.

### **Pathogenesis of fevers.**

Action of exogenous pyrogenes leads to accumulation in blood endogenous pyrogenes. With a current of blood endogenous pyrogenes reach the hypothalamic centers of thermoregulation and influence on thermosensitive neurons preoptic areas forward hypothalamus, activating enzyme phospholipase A<sub>2</sub>. Activation of the given enzyme leads to clearing arachidonic acids from phospholipids of neurons. Then under action of endogenous pyrogenes it is activated cyclooxygenase which directs a metabolism of arachidonic acids on a way of formation of prostaglandin E<sub>2</sub>. Prostaglandins E<sub>2</sub> activate adenylate cyclase, that leads to accumulation 3'-5'/cAMP in cytoplasm of neurons. Accumulation 3'-5'/cAMP increases activity cAMP-dependent protein kinase and of some other enzymes. It leads to reorganization of a metabolism of neurons: excitability cold sensitive neurons increases, and warm sensitive decreases.

Thus, the basic part of pathogenesis fevers - change of excitability central hypothalamic receptors.

↑ sensitiveness of "set level temperature" neurons to the impulses, which comes from neurons of thermostat → real normal signals about the core t° begin to be perceived as information about diminishing t° → braking of heat elimination center and later activating of heat production center

**Braking of heat elimination center** → activating of the sympathetic system → constrict of blood vessels in skin and extremities + contracting smooth muscles which levitate hairs (human has a sign of "goose skin")

**Activating of heat production center** → stimulation of retractive thermogenesis → arise up tone of skeletal muscles and appear shivering → stimulation of nonretractive thermogenesis (action of catecholamines) → ↑ speed of oxidizing processes and basic metabolic exchange

### **Stages of a fever.**

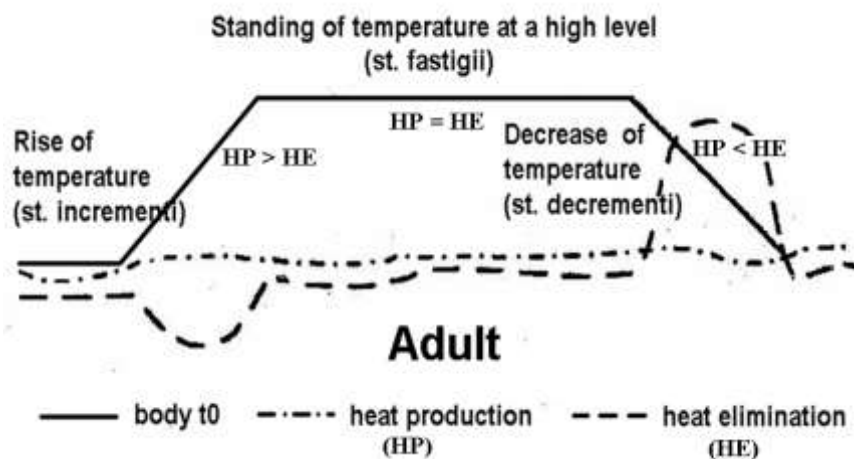
By criterion of change of temperature in development of feverish reaction allocate three stages.

1. **Stage of increase of temperature** (st. incrementi).
2. **Stage of standing of temperature** at a high level (st. fastigii).
3. **Stage of decrease of temperature** (st. decrementi).

### **The characteristic of stages of a fever.**

For the first stage of a fever the positive thermal balance, i.e. prevalence of heat production above heat emission is characteristic. In an organism there is an accumulation of heat. The raised {increased} sensitivity of cold thermoneurons leads to that the organism perceives a normal ambient temperature as lowered. It leads to a spasm of skin vessels, the termination of sweat, the muscular shiver develops. The patient has a fever. Rise of a body temperature can be fast, and a fever very strong and on the contrary, gradual, with an insignificant fever or even without it.





In the second stage there is a formation of balance between heat production and heat emission. The balance between these processes at new, higher level is established {installed}. The body temperature above norm, is supported at one level, but regulation of temperature is kept. The fever stops, develops of arterial hyperemia. Duration of the second stage of a fever depends on character of pathological process.

The Third stage of a fever is characterized by negative thermal

balance, i.e. processes heat emission prevail above heat production. Occurs plentiful of seat due to expansion of skin vessels. heat production decreases due to destruction of microorganisms and destruction of endogenous pyrogenes fermental systems.

Temperature drop can be gradual (*lysis*) and fast (*crisis*). Critical decrease {reduction} in temperature is connected with sharp expansion of skin vessels and can be accompanied by a collapse. Fast temperature drop can be dangerous, especially, at the persons of advanced age transferred a heart attack of a myocardium or having cardiosclerosis. At lytic decrease {reduction} of temperature heat production and heat emission change gradually: heat production inertly decreases, and heat emission gradually comes back to norm.

### The characteristic of a fever

Clinical interpretation of a fever has the important diagnostic value. The doctor should pay attention to following attributes: the beginning, expressiveness, duration of a fever, type of a temperature curve, terms of occurrence and character of organic defeats.

#### 1. The beginning of a fever can be:

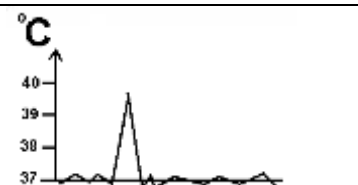
1. **Sharp** (within several hours) - for example, a meningococcus meningitis, ornithosis, leptospirosis
2. **Gradual** (within several days) - for example, a belly typhus, paratyphus

#### 1. On a degree of rise in temperature of a body (expressiveness):

- subfebrile (up to 38°C)
  - Low (up to 37,5°C)
  - High (from 37,6°C up to 38°C)
- febrile (more 38°C)
  - Moderated {Moderate} (up to 39°C)
  - High (up to 41°C)
  - hyperpyrethic (from above 41°C)

#### Temperature curve:

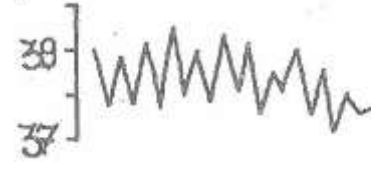



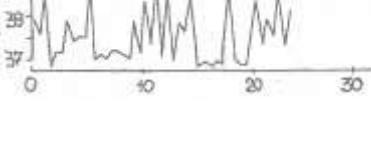



**Passing type** (*febris ephemera*) - unitary short-term "candle" of temperature in some hours. This type is described, for example, at heavy current of a pseudo-tuberculosis and at a delay of milk at not feeding puerpera (a dairy fever).



**Constant type** (*febris continua*) - it is characterized by a heat, without sharp daily fluctuations (no more than 1 degree). It is observed at croupous pneumonias, belly and epidemic typhuss, fever Ky, a pseudo-tuberculosis.





<p><b>Aperient</b> (<i>febris remittens</i>) - similar to a temperature curve of constant type, but has a little more expressed range of <b>daily fluctuations (1-3 degrees)</b>, and, up to the norm temperature does not fall. So occurs in the end of a belly typhus, and sometimes - during all illness. In a similar way can proceed bronchus pneumonia, a tuberculosis, an exudative pleurisy, many <b>virus infections</b> and aseptic fevers.</p>	
<p><b>Alternating</b> (<i>febris intermittens</i>) - the form having greater ranges with decrease of morning temperature up to norm and below, fluctuations 3-4 degrees. Meets at a sharp hepatitis, at a tuberculosis and a sepsis. It is often characterized by separate short-term attacks of rise in temperature is paroxysm, separated from each other the periods of apyrexia. At a malaria attacks can repeat every day (<i>febris quotidiana</i>), or to come in day on the third (<i>febris tertiana</i>) - at infection <i>Pl. vivax</i>, in two days on the fourth (<i>febris quartana</i>) - at infection <i>Pl. malariae</i>.</p>	
<p><b>Returnable type</b> (<i>febris recurrens</i>) - correct alternation of the periods pyrexia and apyrexia lasts some day. An example - a returnable typhus: in this case dependence of a temperature curve on the activator is well visible. Spirochete is phagocytized by macrophages also it is made multiple copies in them. In due course multiplied spirochetes break through a phagocytic barrier and flood blood: to it there corresponds the next attack of a <b>fever</b> lasts during <b>6-8 days</b> then the temperature critically decrease and there comes the period of <b>apyrexia</b> which <b>lasts 6-8 days too</b>. Returnable fevers accompany borreliosis. Aseptic returnable fever is observed at lymphogranulomatosis when the febrile and apyrexia periods alternate and last for 3-10 days. Periodic granulocytopenia is accompanied by episodes of a fever each 3 weeks.</p>	
<p><b>Exhausting, exhausting, hectic</b> (<i>febris hectica</i>) - it is characterized by long current and greater daily <b>fluctuations of temperature (up to 3-5 degrees)</b>. Meets at a <b>sepsis</b>, deep local and system infections, <b>for example</b>, a heavy progressing tuberculosis, <b>malignant tumours</b>. Quite often at a hectic fever there is a distortion of a daily rhythm to morning peaks and evening recession of temperature.</p>	
<p><b>Wrong, atypic</b> (<i>febris irregularis seu atypica</i>) - it is characterized by <b>infringement of a daily rhythm</b>, there are rises in temperature in the mornings and recessions by the evening (<i>febris inversa</i>), or two - three rises and falling, <b>or irregular fluctuations</b> of temperature in current of day. Meets, mainly, at a <b>sepsis</b>.</p>	
<p><b>Wavy or undulating</b> (<i>febris undulans</i>) - it is characterized by <b>gradual increase</b> of a body temperature up to high values and then <b>gradual decrease</b> up to subfebrile (sometimes normal). The cycle repeats through two - three weeks. Meets at infectious (<b>brucellosis</b>, visceral leishmaniasis) and non infectious (lymphogranulomatosis).</p>	
<p>On A.P. Kazantsevu allocate two more types of feverish curves:</p>	
<p>Sharp wavy fever (<i>febris undulans acuta</i>) - unlike undulating, it is characterized by rather short-term waves (3-5 day) and absence of remission between waves - in the form of some fading waves. Meets at ornithosis, a belly typhus, mononucleosis.</p>	
<p>Recurrent (<i>febris recidiva</i>) - unlike a returnable fever, it is characterized usually by one relapse developing various terms (two day - some months). It is observed at leptospirosis, a pseudo-tuberculosis.</p>	

### Positive value of a fever:

1. **Interfere duplication of microorganisms.** It is connected by that at a fever the quantity {amount} of the serum ionized iron (basically due to its linkage with ferritin), the ionized zinc decreases, and concentration of copper increases. The fever reduces stability of activators of diseases to antimicrobial preparations (at temperature 40 °C practically are not made multiple copies of a mycobacterium tuberculosis, gonococcus, treponema, some pneumococcus).
2. **The fever strengthens the immune answer.** There is an activation of specific immunity - development of antibodies, and the nonspecific mechanism of protection - stimulation of phagocytosis increases.
3. The fever **promotes development of some protective factors, such as interferon, lysozyme** (interferon - the unique organismic factor effectively influencing a virus of a flu). At higher, than in norm temperature there is an activation of the endocellular enzymes interfering a reproduction of viruses.
4. At a fever the **general adaptable syndrome develops**, mechanisms hypothalamo-pituitary-adrenal protection join.
5. **Fever often the first and a unique attribute of disease**, therefore supervision over its character - the important element of **diagnostic** tactics of the **doctor**.
6. In most cases the fever provides physiologically justified confinement to **bed sick** (children are exception).
7. It is the **artificial created fever (introduction of pyrogenes) forms conditions for more effective specific treatment of slow diseases ( a bone-articulate tuberculosis, a syphilis, a gonorrhoea, etc.).**

### Negative value of a fever:

1. Increases loading by cardiovascular system (especially, at persons with defeat of the given system).
2. At critical temperature drop undesirable displays of III stage of a fever are possible.
3. Oppression of nervous system.
4. The mediated frustration of functions, organs and systems.
5. Expressed 5 - 7 day time fever for 3-4 weeks switches off spermatogenesis.

### Indications for febrifugal therapy:

Correction of a temperature mode demands the differentiated approach.

1. Hyperthermal fever.
2. Fever at persons with defeat of cardiovascular system.
3. Fever at children of younger age inclined to development of a convulsive syndrome.
4. The separate clinical cases of diseases demanding a specialized estimation (pregnancy, treatment of a bacterial shock, etc.).

### Thermotax at newborns.

Feature of reactance of newborn children, as well as cubs of other mammals, within the first weeks after a birth is a greater intensity untrembling thermogenesis in muscles and, especially, in cells of brown fat .

*Brown fat* settles down in interscapular areas, in mediastinum, along an aorta and large vessels, along a backbone and a sympathetic trunk, under axillary space, in a belly cavity, behind a breast, around of kidneys and adrenal glands and in sucking pads - on cheeks of babies. Brown painting of this type of a fatty tissue is caused by a lot {plenty} of mitochondrias with its ferrikerous painted cytochromes. A brown fatty tissue - the most powerful generator of metabolic heat in an organism. Mitochondrias of brown adipocytes contain protein thermoginin (the activator non phosphorylating oxidations), developed кристы and contact to fine plural liposomes. Cells of brown fat are supplied by a lot of noradrenal receptors and contain sympathetic noradrenergic the nervous terminations.

At newborns in brown fat along a backbone lie paraortic ganglions. Feature of adrenal glands of a fruit is the prevalence of noradrenaline in brain substance (it is kept in current of the first 3-4 months of extrauterine lives). On a signal of hypothalamus sympathetic nerves and хромаффинная tissue of adrenal glands through synapses and blood activate lipolysis and thermogenesis in brown lipocytes. A warming up of blood in large vessels and system effect of free fat acids promote rise in temperature. Blood from congestions of paravertabral brown fat flows through unique anastomoses newborns in a spinal venous sine and warms up spinal thermoensors in segments C5-Th1. It also brakes trembling

thermogenesis at newborns, allowing their muscles to continue tonic activity. The rests of brown fat bring the contribution to mechanisms of temperature adaptation of children till 10-11 years.

Features of thermotax at newborns:

1. *Newborns provide the needs {requirements} in thermogenesis by means of the untrembling mechanism which cannot be found out without special measuring means.*  
Actually development of heat at such children can, without participation of the mechanism of a shiver, to raise on 100-200 % and more in comparison with a level of development of heat in rest. Original mechanisms of temperature adaptation of newborns are very powerful, but the problems facing to them, especially, at prematurity, essentially it is more difficult, than at adults, therefore their homotherm is limited.
2. *The small size of the newborn.* From the point of view of technology thermotax is lack between a surface and volume of a body at prematurity (the newborn approximately three times more, than a corresponding parity {ratio} at the adult).
3. *The superficial layer of a body has no big thickness and the isolating layer of fat is rather thin* (therefore even the maximal narrowing of vessels cannot limit carry of heat from an organism in an environment up to such degree, as at adults). Shortage of brown and white fat at prematurity (and its maintenance at prematurity - no more than 2 % of weight of a body whereas at mature - 8 %) create especially greater problems with thermotax and makes a temperature mode *кювезов* by a basis of an effective survival of prematurity. To solve similar problems, an organism of the mature newborn should increase development of heat in 4-5 times by a mass unit of a body, and an organism of the prematurity child (at weight of 1-1,5 kg.) in 10 times.
4. *Maximal thermotaxic formation and narrowing of vessels at newborns arises at more heat of a skin,* than at adults (nearby 23 0C).
5. *Healthy newborns are rather steady against overcooling* (a limit of therectal temperature compatible to a life, at them below, than at adults - 22-23 0C).
6. *Instability of newborns to overheating is defined {determined} by the limiting mechanisms* connected with small resources of parameters of a water-salt homeostasis.
7. *Newborns allocate cytokine and answer them with a true fever,* however, mechanisms of a fever in the early childhood are characterized by an originality.

**Children are included in group of risk on development of complications at feverish reactions:**

1. In the age of odes 2 months of a life at presence of temperature 38 0C and above.
2. In the age of up to 2 years at temperature above 40 0C (an opportunity of the infectious process caused *Haemophilus influenzae*, *Streptococcus pneumoniae*).
3. All age groups at temperature above 41 0C (probability of a sepsis, a meningitis).
4. With hyperthermal conditions.
5. With a convulsive syndrome in the anamnesis.
6. With heart diseases and vessels.

### **Endogenous anti-pyrogenic system.**

In an organism of the person there is a system endogenous anti-pyrogenic which regulate a level of rise of temperature.

Anti-pyretic factors:

- **arginine-vasopressin mechanism (AVP)** and an **alpha - intermedin hormone** ( $\alpha$ -melanocyte-stimulating hormone, **MSH**). AVP and MSH act on the centers of thermotax, not leaving in a blood-groove, and cause restriction of a fever. In a basis of action AVP lays the neuromodulative mechanism of influence on the thermotax centers, leading elimination of effects activation on periphery due to decrease {reduction} in excitability of coldsensitive neurons. **MSH** - antipyretic effect in 25 000 times higher than in paracetamol.

- **Catecholamines** (adrenaline and noradrenaline)
- **Bombesin** (effect is based on increasing a sensitivity of thermoreceptors in hypothalamus)
- **Thyroliberin**

- **Glucocorticoids** and their inducers (corticotropin-releasing hormone and corticotropin) inhibit a synthesis of pyrogenic cytokines (interleukin-6 and tumor necrosis factor)
- **Pyrogenic cytokines** ( $\uparrow$  pyrogenic cytokines  $\rightarrow$   $\uparrow$  number of **soluble receptors** for these substances  $\rightarrow$  binding of pyrogenic cytokines with their soluble receptors  $\rightarrow$  blocking their binding to receptors on preoptic area of hypothalamus  $\rightarrow$  thus prevents the development of febrile reactions)

### Pyrotherapy.

**Pyrotherapy** (греч.: pyr-fire + therapeia-treatment) - a method of treatment by means of artificial rise in temperature of a body of the patient.

Artificial hyperthermia in medicine it is applied for a long time.

#### History of pyrotherapy.

*A.S.Rozenbljum (1876г.)* - infection with a returnable typhus 12 sick of a progressive paralysis.

*J.Wagner-Яузезы (1887г.)* - infection with a malaria of incurable patients.

*T.Kuli (1893г.)* - application of toxins a Hemolytic streptococcus for treatment of tumours of a head and a neck.

*T.Klyuyev, N.Roskin* - reception a pyrogenic preparation from *Tripanosoma cruzai*.

#### Effects of pyrotherapy.

1. Stimulating action on higher nervous system, симпато-адреналовую systems.
2. Nonspecific, desensibilizative and anti-inflammatory action.
3. Bactericidal effect at diseases of the infectious nature.
4. Stimulation plastic and reparative processes in bones, tissues and parenchymatous organs (at it destruction, damage, etc.).

Pyrotherapy shares on the general and local. The general pyrotherapy is spent by means of pyrogenal or the substances stimulating synthesis of endogenous pyrogens.

*Pyrogenal* is lipopolysacharidum, formed during ability to live of microorganisms *Pseudomonas aeruginosa*. Activity of pyrogenal express in minimal pyrogenous doses. 1 minial pyrogenous dose - the quantity {amount} of substance causing at introduction to rabbits rise in temperature of a body on 0,6 0C and more.

Local therapy is spent in a complex with other methods of treatment for stimulation of immune and not immune protective mechanisms.

### Hyperthermy.

**Hyperthermy** - the typical form of frustration of the thermal exchange, developing in an organism of the person as a result of its sharp increase of heat content, not connected with a fever that is shown by rise in temperature of a kernel of a body above 38 0C and infringement of functions of organs and systems.

**The reasons of hypethermy:** a heat of an environment; the agents interfering realization of mechanisms of heat emission of an organism; isolatives of processes of oxidation and phosphorylation in mitochondrias.

#### Risk factors:

1. Significant humidity of air, air-and water-proof clothes (a combination of humidity and an immovability).
2. Intensive muscular work.
3. Age (old men, children).
4. Diseases (cardiac insufficiency, an arterial hypertension, hyperthyrosis, adiposity, etc.).
5. Smoking, alcoholic intoxication.

### Pathogenesis of hyperthermy.

Action on an organism of various types of heat is realized differently: radiating heat - simultaneously warms up superficial and deep tissues, convection and conduction warmly cause superficial heating tissues, and then-internal organs.

At action of hyperthermal factors in an organism the triad of emergency reactions joins: behavioural, strengthening of processes of heat emission and decrease heat production, stress-reaction. The significant pressure of thermotax mechanisms leads to increase in expenses of energy and to additional rise in temperature of a body, i.e. the vicious circle (circulus vitiosus) is formed. Thus, at hyperthermy

infringement of mechanisms of thermotaxis as a result of an overstrain{overvoltage} and failure of thermotactic systems (unlike a fever) develops.

### **Questions for self-control of knowledge:**

1. Give a definition of superinfections, reinfections.
2. What are the main causes of sepsis?
3. What are sources of pyrogen in infectious process, aseptic tissue damage and immune reactions?
4. What are a mechanisms to reduce heat during fever.
5. What is a significance of temperature-sensitive areas of hypothalamus and peripheral receptors in restructuring of thermoregulation during fever?
6. What are a sources of secondary cells (endogenous) pyrogens?
7. What are a functions of brown fat?
8. What are features of febrile reactions in children?
9. What is a relationship of fever on properties of pyrogenic factor and reactivity of organism?
10. Is a fever is a protective and adaptive response always?
11. What is endogenous antipyrogenous system?
12. What is a mechanism of fever in malignant hyperthermia?
13. Hyperthermia definition. Specify types, stages, mechanisms of development of hyperthermia.
14. Hypothermia: definition. Specify types, stages, mechanisms of development of hypothermia.

### **Tasks for self-managed student work:**

1. Malignant hyperthermia.
2. Endogenous antipyrogenic system.
3. Heat balance in newborns.
4. Phylogeny and ontogeny of febrile reaction.
5. Features febrile reaction in neonatal period and elderly

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### **Compiler:**

senior lector

\_\_\_\_\_ K.A. Kidun







