GM - 21

Federal state budgetary institution of higher education
"North Ossetian state medical Academy"
of the Ministry of health of Russia

Department of pathological physiology

METHODOLOGICAL MATERIALS

for 3rd year students of the medical faculty
by academic discipline

Pathophysiology, clinical pathophysiology

the main professional educational program of higher education - specialty program in the specialty 31.05.01 General Medicine

Part 2

Compilers:
Dzhioev I. G.,
Gadieva V.F.
Tomaeva K.G.

Content.

Regional Blood Flow Disturbances

Numerous disorders of the regional (peripheral, local) blood flow are subdivided into blood flow disturbances in the vessels of medium diameter and blood and lymph flow disturbances in the vessels of microcirculation.

Blood flow disturbances in the vessels of medium diameter can be classified as:

- pathological arterial hyperemia,
- venous hyperemia,
- ischemia,
- stasis.

Arterial hyperemia

Arterial hyperemia is a typical form of violation of the local circulation, characterized by an increase in the blood supply of the organ or tissue due to increased blood flow through the arterial vessels (aorta, arterioles, arteries and arterial capillaries).

Causes

There is a physiological and pathological arterial hyperemia.

Physiological arterial hyperemia

Physiological arterial hyperemia is adequate to the effect and has an adaptive value. It can be functional and protective-adaptive.

1) Functional. It develops in organs and tissues due to an increase in the level of their functioning (for example, hyperemia in a contracting muscle or in a hard working organ).

2) Protective-adaptive. Develops in the implementation of protective reactions and processes (for example, in the focus of inflammation or around an alien transplant, a zone of necrosis or hemorrhage). In these cases, arterial hyperemia contributes to the delivery of oxygen, metabolic substrates, Ig, phagocytes, lymphocytes, other cells and agents necessary for local protective and regenerative reactions in tissues.

Pathological arterial hyperemia

Pathological arterial hyperemia is not adequate to the effect, is not associated with a change in the function of the organ or tissue, and plays a disadaptive, damaging role. Pathological hyperemia is accompanied by impaired blood supply, microhemocirculation, transcapillary exchange, sometimes - hemorrhages and bleeding.

Examples.

Pathological arterial hyperemia of the brain with hypertensive crisis.

Pathological arterial hyperemia of various organs and tissues, developing according to the neuromyocarpathy mechanism [eg, in the organs of the abdominal cavity after ascites; In the skin and muscles of the limb after removing the long-lasting bundle; In the zone of chronic inflammation; In a place of long (several hours) exposure to heat - solar, when using a heating pad, mustard plasters; In the region with sympathetic denervation].

The causes of arterial hyperemia can have a different origin and nature.

By the nature of the causative factor, arterial hyperemia is distinguished by mechanical, physical, chemical, biological and social genesis.

1. Mechanical (mechanical effect).
2. Physical (very high temperature, electric current, local reduction of atmospheric pressure, when setting the cans).
3. Chemical (organic and inorganic acids, alkalis, alcohols, aldehydes).

4. Biological (physiologically active substances formed in the body: adenosine, acetylcholine, prostacyclin, nitric oxide).
5. Social (emotional stress, stress).

By origin, arterial hyperemia is distinguished, the causes of which are endogenous or exogenous factors.

-Exogenous. Agents that cause arterial hyperemia affect the organ or tissue from the outside. These include infectious (microorganisms and / or their endo- and exotoxins) and non-infectious factors of various nature.

- Endogenous. Factors leading to arterial hyperemia are formed in the body [for example, the deposition of salts and concrements in the tissues of the kidneys, liver, subcutaneous tissue; The formation of excess BAA, causing a decrease in the tone of the GMC arterioles (vasodilation), - adenosine, Pg, kinin; Accumulation of organic acids - lactic, pyruvic, ketoglutaric].

Conditions for the development of arterial hyperemia:

1. The site of the action of the stimulus (artery, surrounding its tissues, the corresponding neural formations);
2. The strength and duration of the action of the stimulus. If its action is adequate, then physiological arterial hyperemia arises. If the irritant is extreme - abnormal arterial hyperemia.
3. The state of individual reactivity of the body, sensitization of the body (the state of the autonomic nervous system).

Types of pathological arterial hyperemia according to the mechanism development:

1. Neurotonic or reflex
2. Neuroparalytic
3. Inflammatory arterial hyperemia is due to humoral and reflex mechanisms/
4. Vakat increase blood flow to the discharged space where the air pressure is reduced/
5. Postanemic increased blood flow after ischemia/
6. Postishemic increased blood flow after anemia
7. Collateral arterial hyperemia develops in sudden decrease in blood flow through the main vessel.

Mechanisms of occurrence

The pathogenesis of all types of pathological arterial hyperemia is the same and differs only in the starting moment.

Expansion of the lumen of small arteries and arterioles is achieved due to the realization of neurogenic (neurotonic and neuroparalytic), humoral, neurohumoral and myoparalytic mechanisms or their combination.

1. Neurogenic mechanism. Distinguish between the neurotonic and neuroparalytic varieties of the neurogenic mechanism of arterial hyperemia development.

- Neurotonic mechanism. It is in the predominance of the effects of parasympathetic nervous influences (in comparison with sympathetic) on the walls of arterial vessels.

- Neuroparalytic mechanism. Characterized by a decrease or absence ("paralysis") of sympathetic nerve effects on the walls of arteries and arterioles.

1) Neuroparalytic arterial hyperemia. Etiology: occurs when the tone of the vasoconstrictor centers and nerves decreases. It is known that the sympathetic vasoconstrictor nerves are tonic (impulse in the state of rest 1-2 IU / sec, which determines the vasomotor component of the vascular tone).

In humans and animals, tonic impulsation is inherent in sympathetic nerves, reaching the vessels of the skin of the upper limbs, ears, skeletal muscles, and the food canal. The cutting of these nerves causes a sharp increase in blood flow in each of these organs. This effect is based on the use of

periarterial and ganglionic sympathectomy in the treatment of endarteritis, which is accompanied by prolonged vascular spasms.

In man in the kidneys, brain, lungs, myocardium and some areas of the skin, the vasoconstrictor nerves under normal conditions do not carry tonic impulses and, thus, the transection of the sympathetic nerves of these organs is not accompanied by arterial hyperemia.

Pathogenesis: one of the forms of neuroparalytic arterial hyperemia is hyperemia after previous ischemia, i.e. after the condition of local anemia. In conditions of ischemia, oxygenation of tissues and vessels due to paralysis of the neuromuscular apparatus of the vascular wall is impaired, they lose their tone. If the ischemia stops, the blood begins to flow into this area, but due to the reduced tone of the vasoconstrictors, the arteries sharply expand.

Arterial hyperemia of the neuroparalytic type can also be obtained chemically by blocking the transfer of central nervous impulses to the sympathetic ganglia (with the help of ganglion blockers) or at the level of sympathetic nerve endings (with the help of sympatholytic or adrenolytic drugs).

The neuroparalytic mechanism of arterial hyperemia partially underlies inflammatory hyperemia, ultraviolet erythema, and others.

A classic example of the experimental reproduction of neuroparalytic hyperemia is Claude Bernard's experience, which has received an expansion of the vessels of the rabbit ear after extirpation of the cervical sympathetic nodes.

Also, a frosty blush on the cheeks is a manifestation of physiological neuroparalytic arterial hyperemia. Her mechanism is this: with a decrease in skin temperature, her vessels initially undergo a neurogenic spasm. However, when the skin temperature falls below 15 ° C, due to cold paralysis of neuromuscular excitability and conduction, the dermal vessels begin to expand.

2) Neurotonic arterial hyperemia. Etiology and pathogenesis: neurotonic arterial hyperemia can occur both as a result of irritation of the parasympathetic part of the autonomic nervous system, as well as the redistribution of the sympathetic department. It also appears reflexively in connection with the irritation of the extro- and interoreceptors, the vasodilating nerves and centers under the influence of mental, mechanical, temperature factors, chemical and biological agents. This is the case, for example, with a neuroviral infection caused by herpes zoster, when arterial hyperemia arises in the course of the intercostal nerves. Vasculature-dilating parasympathetic fibers (cholinergic) can be irritated by metabolites that have a vasodilating effect (bradykinin). Since parasympathetic nerve fibers innervate only the vessels of the brain, tongue, salivary glands, external genitalia, bladder and rectum, neurotonic arterial hyperemia is possible in these organs. However, coronary vessels of the heart, cerebral arteries, mucous cheeks, small intestine are innervated by sympathetic nerves (sympathetic vasodilators), the excitation of which also causes hyperemia. Perhaps the development of hyperemia with irritation of sensitive neurons, for example, trigeminal neurons. The resulting hyperemia of the head is associated with the fact that the damaged nerve (inflammation, trauma, neuroinfection) begins to carry out impulses in the opposite direction. Corresponding antidromic effects cause on the periphery a sharp expansion of the vessels of the face, eyeball, change in their permeability. Apparently, such hyperemia is the result of the formation in the nerve endings of the innervated prostaglandin tissue.

Also a classic example of physiological neurotonic arterial hyperemia in humans is the color of shame (or anger) on the cheeks.

2. Neuromyopathy mechanism.

- depletion of catecholamine stores in synaptic vesicles of varicose terminals of sympathetic nerve fibers in the wall of arterioles;
- a decrease in the tone of the smooth muscles of arterial vessels.

- Prolonged action on tissues or organs of various factors of a physical or chemical nature (for example, heat when using heaters, warming compresses, mustard plasters, curative mud, diathermic currents).

- Termination of prolonged pressure on the walls of arteries (for example, ascitic fluid, tight bandage, pressing clothing).

The effect of these factors for a long time significantly reduces or completely removes the myogenic and regulatory (mainly adrenergic) tonus of the walls of arterial vessels. In this regard, they expand, they increase the amount of flowing arterial blood.

Myoparalytic arterial hyperemia is associated with a violation of the tone of the smooth muscles of the vessels (for example, after ischemia, the action of turpentine). The blood is in the vessel expanded after the action of the etiologic factor, which can not be reduced because of the paralysis of the muscular component of the vascular wall. A vivid example of the physiological form of myoparalytic arterial hyperemia is the hyperemia of the cheek at the site of the slap. Since in the trauma vasodilator mediators of inflammation are released, which expand the vessels, acting on the myogenic component of the vascular tone.

3. Vacat arterial hyperemia. Etiology: after removing medical jars.

Pathogenesis: increasing the pressure inside the canal leads to the release of histamine due to the discharge and disruption of the innervation of the vascular wall, which leads to the occurrence of this kind of hyperemia.

4. The humoral mechanism. It is the local increase in the content of vasodilators - biologically active substances with a vasodilating effect (adenosine, nitric oxide, prostaglandin E, prostaglandin E 2, kinin) and in increasing the sensitivity of the receptors of the walls of arterial vessels to vasodilators.

Manifestations of arterial hyperemia

Macroscopic signs

1. The color of the organ and tissue is bright red. Redness of the organ, tissue or their site due to increased arterial blood flow, enlarged arterioles and precapillaries, increased number of functioning capillaries, "arterialization" of venous blood (ie, an increase in the content of HbO2 in venous blood).

2. ↑ t ° (on the surface of the body). Increase in temperature of tissues and organs in the region of hyperemia as a result of influx of warmer arterial blood and increase in metabolic rate.

3. An increase in the organ or tissue in size. Increase in the volume of the organ or tissue as a result of an increase in their blood - and lymphatic filling.

4. ↑ turgor Increased organ or tissue turgor as a result of the increase in their blood - and lymphatic filling.

5. Swelling develops rarely

Microscopic signs:

1. Increase in linear and volumetric flow velocity. Reduction of the diameter of the axial "cylinder" (the flow of blood cells along the central axis of the arteriola) and an increase in the width of the blood plasma flow with a small content of shaped elements around it around this "cylinder". The reason: an increase in centripetal forces and the rejection of blood cells to the center of the lumen of blood vessels in connection with the acceleration of blood flow in conditions of arterial hypertension.

2. ↑ Pressure in arterial vessels

3. Increase in the diameter of small arterial vessels, capillaries and venules.

4. ↑ the number of functioning capillaries (ie, capillaries, through which the plasma and blood elements flow).

5. ↑ Pressure in venous vessels (not always)

6. Increase in lymphogenesis and lymph flow due to increased perfusion pressure of blood in the vessels of the microcirculatory bed.

onsequences of arterial hyperemia

In the case of physiological varieties of arterial hyperemia, the activation of a specific function (function) of the organ or tissue and the potentiation of their nonspecific functions and processes are noted.

Examples: activation of local immunity (due to increased influx with arterial blood of Ig, lymphocytes, phagocytic cells and other agents), acceleration of plastic processes, increased lymphocyte formation and lymphatic drainage from tissues.

Provision of hypertrophy and hyperplasia of structural elements of tissues by metabolic products and oxygen.

Achieving precisely these effects of arterial hypertension becomes a goal in the conduct of therapeutic measures (for example, with the use of compresses, mustard plasters, physiotherapeutic procedures, injections of vasodilating drugs, surgical interventions for the intersection of sympathetic nerve trunks or excision of sympathetic ganglia in certain forms of angina, etc.) Aimedt inducing hyperemia. This is used for damage to organs and tissues, their ischemia, disturbance of trophic and plastic processes in them, decrease in the activity of "local immunity".

In pathological variants of arterial hyperemia, as a rule, overgrowth and micro-rupture of the walls of the vessels of the microcirculatory bed, micro- and macroclorogenesis in the tissue, bleeding (external and / or internal) are observed.

Elimination or prevention of these negative consequences is the goal of therapy of pathological varieties of arterial hyperemia.

Venous Hyperemia

Venous hyperemia is a typical form of local circulatory disturbance, characterized by an increase in the blood supply of the organ or tissue due to a decrease in the outflow of blood through venous vessels (venules, veins, and venous type capillaries).

Causes

1. A mechanical obstacle to the flow of venous blood from tissues or organs. This may be the result of a narrowing of the lumen of the venule or vein when it is compressed (swelling, edematous tissue, scar, tourniquet, tight bandage) and obturation (thrombus, embolus, tumor); Heart failure; Low elasticity of the venous walls, combined with the formation in them of extensions (varicosities) and constrictions.
2. Physical (the effect of changed temperatures).
3. Chemical (taking hormonal contraceptives contribute to the development of thrombophlebitis and the progression of venous diseases).
4. Biological (clogging of vessels with helminths and others).
5. Social (professions associated with excessive presence in the vertical position - surgeons, hairdressers and others).

Conditions:

1. The strength of the stimulus.
2. The site of the stimulus (vessels of venous type).
3. Time of action of the stimulus.
4. The initial state of the body for the duration of the action of the stimulus.
5. Condition of the venous collateral network.

By the mechanism of development, obturative, compression, neuro-reflex (decrease in vasoconstrictor influences on veins), congestive, orthostatic are distinguished.

The mechanism of development

Violation or obstruction of blood flow leads to an increase in the blood filling of capillaries, post-capillaries and venules, the formation of microthrombi and pendular movement of blood

(during the systole of the blood, the blood jerks along the vessels, the diastolic blood moves in the opposite direction, starting from the obstruction - embolus, thrombus, squeezed walls Vessels). As a result, the permeability of the vascular wall increases, the fluid goes beyond the vessel, edema develops. The consequence of stopping blood flow are micro - and macronecrosis, the main cause of which is oxygen starvation and metabolic disorders. With prolonged edema, the parenchyma of the organ dies, and the stroma grows (elephantiasis).

Manifestations

1. Increase in the number and diameter of the lumen of venous vessels in the region of hyperemia.

2. Cyanosis of tissue or organ due to an increase in the amount of venous blood in them and a decrease in the content of the venous blood of HbO2. The latter is the result of the utilization of oxygen by tissue from the blood in connection with its slow current through the capillaries.

3. Decrease in temperature of tissues or organs in the zone of venous stasis as a result of an increase in the volume of venous blood in comparison with arterial blood and a decrease in the intensity of tissue metabolism (the result of a decrease in arterial blood flow to tissues in the region of venous hyperemia).

4. Edema of the tissue or organ occurs due to increased intravascular pressure in capillaries, postcapillaries and venules. With prolonged venous hyperemia edema is potentiated due to the inclusion of its osmotic, oncotic and membranogenic pathogenetic factors.

5. Hemorrhages in the tissue and bleeding (internal and external) as a result of overstretch and microfractures of the walls of venous vessels (postcapillaries and venules).

6. Changes in the vessels of the microvasculature.

- Increase in the diameter of capillaries, postcapillaries and venules as a result of stretching the walls of microvessels with excess venous blood.

- Increase in the number of functioning capillaries at the initial stage of venous hyperemia (as a result of outflow of venous blood through previously dysfunctional capillary nets) and a decrease in later capillary networks (due to the cessation of blood flow due to the formation of microthrombi and aggregates of blood cells in postcapillaries and venules).

- Slow down (until termination) of outflow of venous blood.

- Significant expansion of the diameter of the axial "cylinder" and the disappearance of the plasma current band in venules and veins.

- "Pendulum" movement of blood in venules and veins - "back and forth": "There" - from the capillaries to venules and veins, the reason is: carrying out a systolic wave of cardiac blood ejection; "Back" - from the veins to the veins and capillaries, the reason: "reflection" of the flow of venous blood from a mechanical obstruction (thrombus, embolus, narrowed venules).

Pathogenic effects of venous hyperemia

Venous hyperemia has a damaging effect on tissues and organs due to a number of pathogenic factors.

The main pathogenic factors: hypoxia (circulatory type at the beginning of the process, and for a long flow - mixed type), edema of the tissue (due to increased venous and venous pressure on the wall), hemorrhages in the tissue (as a result of overstretch and rupture of postcapillary walls and venules) and bleeding (internal and external).

We can also highlight a number of positive effects for the body. In particular, it can include discharge of the heart with heart failure, a decrease in the outflow of toxins, the products of decay of tissues when they are damaged, the development of connective tissue - scar in hard-healing ulcers.

Consequences: reduction of specific and nonspecific functions of organs and tissues, hypotrophy and hypoplasia of structural elements of tissues and organs, necrosis of parenchymal cells and development of connective tissue (sclerosis, cirrhosis) in organs.

Ischemia

Ischemia is a typical form of violation of the local circulation, characterized by a decrease in the blood supply to the body, organ or tissue, due to the reduction or cessation of blood flow through the arterial vessels.

Causes

The causes of ischemia can have different origins and nature.

By nature, the causes of ischemia are divided into physical, chemical and biological.

1. Physical factors: compression of arterial vessels (eg, swelling, scar tissue, foreign body, tourniquet), narrowing or closing the lumen from the inside (eg, thrombus, embolus, atherosclerotic plaque), excessively low temperature.
2. Chemical factors. Many chemical compounds have the ability to cause a decrease in the MCA of arterial vessels and a narrowing of their lumen. Examples: nicotine, a number of medicines (mezaton, ephedrine, adrenaline preparations, ADH, angiotensins).
3. Biological factors: BAS with vasoconstrictive effects (for example, catecholamines, angiotensin II, ADH, endothelium), BAS of microbial origin: their exo and endotoxins, metabolites with vasoconstrictive action.
4. Physical factors (effects of altered ambient temperatures).
5. Social factors (stressful emotional factors).

By origin, isolated ischemia, the cause of which is endogenous or exogenous (infectious and non-infectious).

Conditions conducive to the development of ischemia:

1. The stimulus
2. Time of action
3. Place of action (artery, microvessels of arterial type)
4. Condition of arterial-collateral circulation.

Types of ischemia by mechanism of origin

1. Compression ischemia
2. Obturation ischemia
3. Neurogenic (angiospastic) ischemia
4. Collateral ischemia (with the development of arterial hyperemia in the collateral area).
5. Obliterative ischemia.

Mechanisms of occurrence of ischemia

I. Mechanisms that determine the predominant decrease in arterial blood flow to tissues and organs: neurogenic, humoral and mechanical.

1) Neurogenic mechanism (neurotonic and neuroparalytic).

- Neurotonic. Characterized by the predominance of the effects of the sympathetic nervous system on the walls of arterioles compared with parasympathetic. This is accompanied by an increased release of norepinephrine from adrenergic terminals.

Causes: activation of sympathetic influences on tissues and organs (for example, in various types of stress, action on low temperature tissue, mechanical trauma, chemicals) and increasing adrenoreactive properties of arteriolar walls (for example, when they are sensitized to vasoconstrictor agents - in conditions of elevated Ca2 + Or cAMP in myocytes).

- Neuroparalytic. It is characterized by the elimination or reduction ("paralysis") of parasympathetic influences on arteriolar walls.

Cause. The inhibition or blockade of nerve impulses along the parasympathetic fibers to the arterioles (and in connection with this - the release of acetylcholine from the terminal nerve fibers in the walls of the arteries, arterioles and precapillaries). Such a situation can be observed with

neuritis, mechanical trauma, tumor development, surgical removal of ganglia or the intersection of parasympathetic nerves.

2) The humoral mechanism. It consists in increasing the content of substances with vasoconstrictive action (eg, angiotensin II, ADH, thromboxane A2, adrenaline, nrF) in the tissues of the substances and the sensitivity of arteriolar wall receptors to agents with vasoconstrictive action (for example, with increasing in tissues [Ca2 +] or [Na +]).

3) Etiological factor of a mechanical nature. Characterized by the presence of a mechanical obstacle to the movement of blood through the arterial vessels.

Causes: compression (compression) of the arterial vessel with a tumor, scar, edematous tissue, a tourniquet and a decrease (until the closure is complete) of the arteriolar lumen (eg, blood clot, aggregate of blood cells, embolus).

II. The mechanisms of occurrence of ischemia, which mainly lead to a significant increase in tissue consumption of oxygen and / or substrates of metabolism. At the same time, the need for oxygen and substrates of metabolism exceeds the level of their real delivery to the tissues.

The most common reason: a significant increase in the function of the organ or tissue and the increase in this regard the intensity of the metabolism in them.

Examples.

- Ischemia of muscles (including myocardium) with intensive and prolonged physical activity. - Myocardial ischemia with acute significant increase in blood pressure (for example, in conditions of hypertensive crisis) and emotional stress.

In the latter case, the work of the heart increases significantly under the influence of excess catecholamines, which cause positive chrono and inotropic effects. In these conditions, the flow of blood to the myocardium along the coronary arteries also increases. However, the work of the myocardium (and, in accordance with this, the need for blood supply) increases to a greater extent. Myocardial ischemia is developing, manifested by an attack of angina pectoris, and often the death of an ischemic heart segment (myocardial infarction).

Simultaneously, as a rule, signs of narrowing of the arterial vessels of the heart are revealed in connection with the development of atherosclerotic changes in them.

<u>Macro and microscopic signs of ischemia:</u>

1. Pale.
2. Disturbance of sensitivity.
3. Pain.
4. Reduction of the volume and turgor of a tissue or organ site.
5. Decrease in linear and volumetric flow velocity.
6. Decrease in pressure in arterial vessels.
7. ↓ diameter of small arterial vessels, capillaries and venules.
8. ↓ number of functioning capillaries.
9. ↓ Vascular ripples.

10. ↓ pressure in the venous vessels.
11. Decreased lymphatic and lymphatic drainage.
12. Lowering the temperature of the part of the organ or tissue.

Consequences of ischemia

The nature, severity and scale of the consequences of ischemia depend on many factors. The most significant are:

- The rate of development of ischemia (the higher it is, the more significant the damage to tissues).
- The diameter of the affected artery or arterioles (the larger it is, the heavier the lesion).
- "Sensitivity" of tissue or organ to ischemia (it is especially high in brain tissue, heart, kidneys).

- The importance of an ischemic organ or tissue for the body (the ischemia of organs such as the brain, heart, kidneys, can lead to the death of the body, in contrast, the ischemia of the skin or any skeletal muscle is compatible with life).
- The degree of development of collateral vessels and the rate of inclusion or activation of collateral blood flow in the tissue or organ.

Collateral blood flow is the circulatory system in the vessels around the ischemic tissue site and in it.

1. The presence (or increase) of the collateral circulation is facilitated by the presence of a blood pressure gradient above and below the narrowed portion of the vessel, accumulation in the ischemia of BAS with vasodilating action (adenosine, acetylcholine, Pg, kinin, etc.), activation of local parasympathetic influences (contributing to the expansion of collateral Arterioles) and a high degree of development of the vasculature (collaterals) in the affected organ or tissue.

2. Groups of organs and tissues, depending on the degree of development of arterial vessels and anastomoses between them.

- With an absolutely sufficient collateral network: skeletal musculature, mesentery of the intestine, lungs. In these formations, the total lumen of the collateral vessels is equal to or greater than the diameter of the main artery. In connection with this, the cessation of blood flow along it does not cause severe tissue ischemia in the region of blood supply of this artery.
- With absolutely insufficient collateral: myocardium, kidneys, brain, spleen. In these organs, the total lumen of the collateral arteries is much smaller than the diameter of the arterial branch. In this regard, its occlusion leads to severe ischemia or a tissue infarction.
- With relatively sufficient (insufficient) collaterals: the walls of the intestine, stomach, bladder, skin, adrenal glands. In them, the total lumen of the collateral vessels is more or less pronounced than the diameter of the main artery. Occlusion of a large arterial trunk in these organs is accompanied by a greater or lesser degree of their ischemia.

STASIS

Stasis is a significant slowing or cessation of the flow of blood and / or lymph in the vessels of the organ or tissue.

Causes

1. Ischemia and venous hyperemia. They lead to stasis due to a significant slowing of blood flow (with ischemia due to a decrease in arterial blood flow, with venous hyperemia as a result of slowing or cessation of its outflow) and creating conditions for the formation and / or activation of substances that cause the gluing of blood cells, Aggregates and thrombi.
Proagregantes are factors that cause aggregation and agglutination of blood elements.

Pathogenesis

Etiological factors

↓

Activation and / or increase in blood levels

↓

Proagregants, cations, large-molecule proteins

↓

Adhesion, aggregation, agglutination of blood elements

↓

Slowing or stopping the flow of blood and / or lymph in the vessels

↓

Stasis

At the final stage of stasis, there is always a process of aggregation and / or agglutination of blood cells, which leads to a thickening of blood and a decrease in its fluidity. This process activates pro-aggregates, cations and high-molecular proteins.

Proagregantes (thromboxane A2, adenosine diphosphate, nrF, Pge, catecholamines, antibodies to blood elements) cause adhesion, aggregation, agglutination of blood elements with subsequent lysis and the release of biologically active substances (including proaggregants, potentiating aggregation and agglutination reactions).

Cations. K +, Ca2 +, Na +, Mg2 + are released from blood cells, damaged walls of blood vessels and tissues. Adsorbed on the cytolemma of the formed elements of blood, an excess of cations neutralizes their negative surface charge or even reverses it. And if undamaged cells (due to negative charge) "repel" from each other, the damaged cells ("neutralized") form aggregates. Even more actively aggregate "recharged" blood cells. Having a positive surface charge, they come close to the "neutralized" cells and especially with the damaged ones (having a negative charge), forming aggregates adhering to the intima of the vessels.

High-molecular proteins (eg, y-globulins, fibrinogen) remove the surface charge of intact cells (by connecting to the negatively charged cell surface with amino groups having a positive charge) and potentiate the aggregation of the blood elements and the adhesion of their conglomerates to the wall of the vessel (achieved by fixing a large The number of protein micelles with adhesive properties on the surface of the blood cells).

Types of stasis

All varieties of stasis are divided into primary and secondary.

Primary (true) stasis. Formation of stasis primarily begins with the activation of blood elements and the allocation of a large number of proagregants and / or procoagulants. In the next step, the shaped elements aggregate, agglutinate and attach to the wall of the microvessel. This causes a slowing or stopping of blood flow in the vessels.

Secondary stasis (ischemic and congestive).

- Ischemic stasis develops as an outcome of severe ischemia due to a decrease in the influx of arterial blood, a slowing of the speed of its current, its turbulent nature. This leads to aggregation and adhesion of blood cells.

- Stagnant (venous-stagnant) stasis is the result of slowing down the outflow of venous blood, condensation of it, changes in physico-chemical properties, damage to blood cells (in particular, due to hypoxia). Subsequently, blood cells adhere to each other and to the wall of microvessels.

Manifestations of stasis

When stasis, characteristic changes occur in the vessels of the microcirculatory bed:

- a decrease in the internal diameter of microvessels with ischemic stasis,
- an increase in the lumen of the vessels of the microcirculatory bed with stagnant stasis,
- a large number of aggregates of blood elements in the lumen of the vessels and on their walls,
- microcirculation (more often with stagnant stasis).

At the same time, manifestations of ischemia or venous hyperemia may overlap with stasis.

Consequences of stasis

With the rapid elimination of the cause of stasis, the blood flow in the vessels of the microcirculatory bed is restored and no significant changes develop in the tissues.

Prolonged stasis leads to the development of dystrophic changes in tissues, often to the death of a tissue or organ site (infarction).

Thrombosis

Thrombosis (from Greek thrombsis - coagulation), lifelong formation of blood clots (thrombi) in the lumen of the vessels or in the cavities of the heart. It is the most important cause of local circulatory disorders: ischemia and venous hyperemia. In addition, 99% of the embolism is caused by thrombi or parts thereof, the so-called thromboembolism.

Analyzing this definition, it is necessary to pay attention to the following two points. First, thrombosis is an intravital phenomenon, differing from the postmortem blood clotting. The thrombus is fixed on the vascular wall, and the postmortem clot of blood lies in the lumen of the vessel freely and can be easily removed from it. This circumstance is important in forensic medicine, when it is necessary to establish the cause of death and the time of its onset. Secondly, thrombosis is not only the clotting of blood, but a complex process that involves a number of stages and leads to the formation of a dense mass consisting of blood elements in the lumen of the vessel. Blood coagulation is only one of the components of thrombosis.

Causes of thrombosis

1. Physical factors - the effect of electric current.
2. Chemical factors - adrenaline releases inhibit the synthesis of prostaglandin (prostaglandin slows blood clotting), thereby promoting thrombosis; Taking hormonal preparations (for example, contraceptives); Smoking contributes to the formation of nicotine thromboxane - a powerful regulator of blood coagulability.
3. Mechanical factors - mechanical damage to the vessel wall.
4. Biological factors - the effect of endotoxins of microorganisms; Childbirth; Atherosclerosis, diabetes mellitus, hypertension, allergies; the process of the appearance of tumors (development of benign and malignant tumors) promotes thrombus formation.
5. Social factors - sedentary lifestyle contributes to inadequate blood circulation and can cause pulmonary embolism or venous thrombosis.

Conditions for thrombus:

1. The strength of the stimulus.
2. Place of action.
3. Time of action.
4. The initial state of the body at the time of the action of the stimulus.

The main conditions contributing to intravascular coagulation (and, hence, thrombosis) were formulated by Rudolf Virkhov in the middle of the last century and were called the triad of Virchow or a cause-and-effect relationship in the mechanisms of thrombus formation:

1. Damage of the vascular wall;

In a normal blood vessel with an intact wall, laminar blood flow is observed when layers of blood slide relative to each other linearly. If the integrity of the vessel wall is disturbed at the site of this damage, the laminar flow is replaced by turbulent flow, that is, turbulence develops, which contributes to the retention of the formed blood elements near the vascular wall and forms the basis for the formation of a thrombus.

If the vascular wall is damaged, this part of it becomes wettable, that is, drops of liquid begin to adhere to the wall of the vessel. This also contributes to fixing on it the uniform elements of blood.

Normally, the blood cells and vascular wall have the same electrical charge, which leads to their mutual repulsion. At the site of damage, the vascular wall loses its charge, due to which the formed elements of blood settle on this place.

When the vessel wall is damaged from it, tissue thromboplastin is released into the bloodstream, which, reacting with other coagulation factors, gives a push of blood coagulation, and is also necessary for the formation of a thrombus.

2. Violation of the activity of coagulating and anticoagulating blood systems. Changes in the physico-chemical properties of blood, leading to an increase in its coagulability. For example, with a disease such as erythremia, which significantly increases the number of all blood cells, including blood platelets - platelets, and increases the viscosity of the blood, very often there is a generalized thrombosis of the vessels, from which the patient dies.

3. Slowing of blood flow. The faster the blood flow in the vessel, the harder it is to hold the shaped elements near the vascular wall, even despite its damage. For example, with severe atherosclerosis, the wall of the ascending aorta is most severely damaged. However, in this part of the aorta, thrombi are very rare, since the blood flow velocity is so high that the beginning clot forms all the time from the wall and is carried away by the blood flow. The most common thrombi form in the veins, where the blood flow is sharply slowed. Therefore, any factor that causes a slowing of blood flow in the vessels, will promote thrombogenesis.

However, both of these factors remain only conditions conducive to thrombosis, but no more. If there is no damage to the vascular wall, a thrombus is not formed, even if the blood flow in the vessel is slowed and the physicochemical properties of the blood have changed. And only damage to the vessel wall is the initiating moment of thrombus formation.

There are three types of thrombi:

1. White (agglutinative) thrombus. In its formation, the main role is played by the processes of agglutination (gluing) of the blood elements, mainly platelets, leukocytes and fibrin. This thrombus is formed slowly with a rapid flow of blood (more often in the arteries).

2. Red (coagulative) thrombus. In its formation, the main role is played by the processes of coagulation (coagulation) of blood. In the loops of fibrin, in the formation of this thrombus, erythrocytes are retained in large quantities, so this thrombus is red, formed rapidly with a slow blood flow (usually in the veins).

Since the coagulation process proceeds faster than the agglutination process, the red blood clot forms more rapidly than the white clot. Therefore, in emergency situations, when rapid formation of a thrombus is required (for example, with bleeding), red blood clots are predominantly formed.

3. Mixed thrombus. It occurs most often. In the formation of this type of thrombus, processes of agglutination and coagulation alternately take part. On a cut, this thrombus has a layered character. The head of the mixed thrombus, that is, its part attached to the vascular wall, is usually white, the body is layered, and the tail is red.

4. Hyaline thrombus.

Hyaline thrombus usually consists of destroyed erythrocytes, platelets, precipitating plasma proteins, rarely contain fibrin. Thrombotic masses resemble hyaline. Such thrombi are found in the vessels of the microcirculatory bed.

Depending on the size of the lumen in the vessel, distinguish:

1. The parietal thrombus is often found:

- in the heart on the valve or parietal endocardium with its inflammation (thromboendocarditis);
- in the ears and between the trabeculae in chronic heart failure (heart disease, chronic ischemic heart disease);
- in large arteries with atherosclerosis;
- in the veins with their inflammation (thrombophlebitis), in aneurysms of the heart and blood vessels.

2. Clogging (occlusive) thrombus is formed more often:

- in the veins and small arteries with the growth of the parietal thrombus,
- less often - in large arteries and aorta.

Mechanisms of hemostasis, underlying the thrombosis.

In the process of thrombosis, four stages are distinguished:

Stage 1 - cell (adhesion, aggregation and agglutination of platelets);

Stage 2 - coagulation (plasma coagulation phase (thrombin formation, fibrin formation)); Stage 3 - retractions (compaction).

4 stage - the outcome.

The degree of impaired function of the organs in thrombosis depends on its outcome, which can be as follows:

1. Organization of thrombus, ingrowth into thrombus and replacement with its connective tissue; Leads to a decrease in lumen or complete occlusion of the vessel, a violation of blood flow and the development of ischemia or venous hyperemia (depending on where the thrombus was located - in the artery or vein).

2. Closure of the thrombus and its transformation into embolus. In this case, the severed thrombus is transferred by a current of blood to other regions of the body and clogs the vessel through which it can not pass, and causes disturbances in the local circulation in this area.

3. Organization - recanalization - can develop in the process of organizing a thrombus due to incomplete replacement of thrombus with connective tissue, which leads to inferior restoration of blood flow in the vessel and pathological changes in the vascular wall; In the veins, there is often a violation of the structure of the valves, their insufficiency, which is the cause of further development of venous hyperemia (for example, with thrombophlebitis of the veins of the lower extremities and the development of postthrombophlebitic syndrome).

4. Septic, purulent melting of the thrombus. When a thrombus is infected in the area where it is located, purulent inflammation can begin. From a clot will begin to come off pieces and turn into emboli. In addition to hemodynamic disorders, which these emboli cause, by clogging small vessels, they will promote the dissemination of microorganisms to various organs and tissues.

5. Aseptic melting. Thrombotic resorption leading to restoration of blood flow in the vessel. In this case, the degree of disruption of tissue function will depend on the duration of the ischemia process until the complete resolution of the thrombus.

Evaluation of thrombosis for the body should be carried out from two positions. First of all, thrombosis is a physiological process aimed at stopping bleeding from a damaged vessel. However, with a pathological change in the walls of blood vessels, thrombosis from a protective-adaptive reaction turns into pathological, leads to the development of often very severe disorders of local circulation, which can result in disability or even death of the patient.

Positive and negative value of thrombosis for the body. It should be noted that thrombosis, like many other processes in the body (inflammation, pain, etc.), from the standpoint of biological expediency should be considered dialectically. On the one hand, thrombosis is a protective-adaptive

reaction, since it performs a biologically expedient role for the organism, especially in cases when it is triggered by local, more exogenous, damage to the vascular wall, without which the existence of the organism would be absolutely impossible, since any bleeding Would be fatal.

On the other hand, in pathological conditions in which thrombosis is triggered by the action of endogenous (for example, alteration of the vascular wall in atherosclerosis, hyperkatecholamineemia, release of proteolytic enzymes as a result of activation of the complement system in an allergic reaction, etc.) or exogenous factors of extreme strength (multiple trauma , Severe stress), it becomes the cause of severe and even fatal complications (myocardial infarction, pulmonary thrombosis, ischemic gangrene of the extremity, etc.), which allows Consider thrombosis as a pathological process. The consequences of such thrombosis are extremely unfavorable for the body, although the initial phase of pathological thrombus formation develops as a result of the same causes as the process of normal blood clotting.

The consequences of thrombosis: thromboembolism, ischemia, venous hyperemia, ischemic or venous infarction, gangrene.

echanisms of hemostasis

Hemostasis is the stopping of bleeding with damage to blood vessels. Mechanisms that provide hemostasis are realized not only with bleeding, but also with any damage to the endothelium of the vascular wall caused by physical (for example, catheterization), hemodynamic, chemical factors, inflammation, immune complexes, metabolic disorders (atherosclerosis, collagen diseases) E. Hemostasis is achieved mainly due to the formation of thrombus as a result of the interaction of plasma components, platelets and the vascular wall.

In this case, both parietal and intramural thrombosis can develop. Functional inferiority of the hemostatic system can lead to local or generalized bleeding.

There are two mechanisms of hemostasis: platelet-vascular (primary) and coagulation (secondary).

The predominance of this or that mechanism depends mainly on the caliber of the damaged vessel and the rate of blood flow. However, effective hemostasis is possible only with the normal functioning of both mechanisms.

Thrombolytic-vascular hemostasis. The stop of bleeding with damage to the vessels of the microcirculatory bed is due to spasm of blood vessels and the formation of a platelet thrombus. The totality of these processes is the essence of thrombolytic-vascular hemostasis.

To damage microvessels respond with a short-term spasm, resulting in bleeding from them in the first 20-30 s. Does not arise. This vasoconstriction is caused by reflex spasm of blood vessels due to contraction of smooth muscle cells of the vascular wall and is maintained by vasospastic agents secreted by endothelium and platelets - serotonin, noradrenaline, adrenaline.

Normally, the number of platelets ranges from 150 x 109 / L to 400 x 109 / L, the normal life span of the platelet after ligation from the megakaryocyte is 6-10 days, in addition, 15-25% of the platelets are absorbed daily by the vascular endothelium, which provides angiotrophic and endotheliocyte support Function of thrombocytes. They promote endothelialization at the site of damage involving the secretion of growth factors.

In the formation of a thrombocytic thrombus, several consecutive stages are isolated:

- activation of platelets and adhesion of platelets to the vascular wall;
- aggregation of platelets;
- Release reaction;
- Compaction of platelet thrombus.

Activation and adhesion of platelets. When the vessels are damaged, there is a buildup of platelets in this zone and their interaction with subendothelium elements - collagen and microfibrils. After 1-2 seconds after injury, platelets adhere to the vascular wall. This represents the initial period of platelet thrombus formation.

The most pronounced adhesive properties are collagen I and III types and von Willebrand vascular wall factor, to which there are receptors on the surface of still unactivated platelets. In the process of adhesion, the shape of platelets changes, from disc-shaped they become transformed into prolate process cells-activated platelets. Adhesion of platelets to the subendothelium is facilitated by a slowing of the blood flow, aggregation of erythrocytes, an increase in the viscosity of the blood, an increase in the plasma content of large-dispersed proteins and lipids.

Aggregation of platelets. Along with adhesion, aggregation of platelets occurs, ie, their connection with each other and the formation of conglomerates (aggregates) of different sizes and densities. The aggregation inductors are arachidonic acid, thrombin, thromboxane A2, collagen, adenosine diphosphate (ADP), serotonin, adrenaline, noradrenaline. Thrombin, arachidonic acid, collagen stimulate the secretion of the contents of granules of platelets - the "release" reaction and the synthesis of cyclic endoperoxides in platelets, including thromboxane A2. Serotonin and thromboxane A2 also have vasoconstrictor properties.

In the platelets there are granules of four types - dense (type 1), a-granules (type 2), peroxisomes (type 3), lysosomes (type 4). During the release reaction, the α-granules release the following: (i-thromboglobulin, platelet factor 4, von Willebrand factor, platelet growth factor, antiheparin factor, adrenaline, serotonin and ADP causing dense platelet aggregation from dense

ranules, from peroxisomes and lysosomes - such Enzymes, such as arabinosidases, acid hydrolases, proteases.

In the process of platelet aggregation, two phases are distinguished: reversible and irreversible.

The first phase - the formation of loose platelet aggregates of 10-15 platelets with pseudopodia. Such platelet aggregates are easily destroyed and carried away by a current of blood. These aggregates do not provide complete hemostasis. At this stage, spontaneous disaggregation under the influence of ATP, AMP, adenosine, fibrinogen degradation products and fibrin is possible.

The most pronounced disaggregating effect is prostacyclin (PG 12), which is formed predominantly in the endothelium of vessels from cyclic endoperoxides, including platelets, under the influence of prostacyclininsyntase. Prostacyclin stimulates platelet adenylate cyclase, which is accompanied by the accumulation of cAMP and inhibition of aggregation. The half-life of prostacyclin is about 2 minutes. Prostacyclin also has vasodilatory properties. Unlike other prostaglandins, prostacyclin is not inactivated in the lungs. The concentration of prostacyclin in the blood is low, but this is quite enough to prevent the formation of platelet aggregates in the bloodstream and disaggregation of platelets at the site of vascular injury.

The second phase of irreversible aggregation - the formation of persistent platelet aggregates occurs at a high concentration of substances that cause aggregation, and also at the action of low concentrations of such aggregates, which have a pronounced stimulating effect and activate the release of platelet granules (thrombin, arachidonic acid, thromboxane A2, collagen). In the mechanism of platelet aggregation, an extremely important role is played by cyclic endoperoxides and thromboxanes. Under the influence of inducers of aggregation of collagen and thrombin, phospholipase A2 of the platelet membrane activates, which ensures the activation of the process of lipid peroxidation, leading to the cleavage of membrane phospholipids. As a result, the arachidonic cascade is activated and cyclic endoperoxides - prostaglandins (nFG2 and PGH2) and thromboxanes A2 and B2 are formed. These prostaglandins and thromboxanes, especially thromboxane A2, are powerful inducers of aphasia. Under the influence of thromboxane A2, adenylate cyclase of platelets

is inhibited, cAMP formation decreases, intracellular concentration of Ca2 + ions increases, phosphotidylinositide pathway of hydrolysis of phospholipids of membranes is activated, and platelet aggregation occurs.

Under normal conditions, the formation of platelet cyclic endoperoxides and thromboxanes is insignificant. In the mechanism of limiting the biosynthesis of these thrombogenic substances, cAMP plays the leading role, which regulates the concentration of intracellular Ca2 + through the protein kinase system and inhibits the phospholipase A2. When the cAMP content in platelets increases, their aggregation is inhibited, and when it decreases, it increases. Active influence on lipid peroxidation and platelet cAMP exchange is one of the ways of pharmacological correction of platelet aggregation.

Under conditions of aggregation, a decisive role is played by thrombin, which is secreted from platelets and formed during coagulation hemostasis. Thrombin quickly activates irreversible platelet aggregation, which ends with a viscous metamorphosis, a complex of morphological and biochemical changes in platelets, including the formation of strong bridges between them, an increase in membrane permeability, degranulation, and cell destruction.

During the aggregation, the contractile protein of platelets, thrombostenin, is activated. With his participation there is a change in the form of platelets and their maximum approximation to each other in aggregates that become dense and impermeable to the blood. The formation of a stable platelet thrombus is facilitated by the filaments of insoluble fibrin formed in the zone of damage to the vascular wall. Tissue thromboplastin (factor III) of the vascular wall interacts with plasma clotting factors and as a result, thrombin is formed, which converts fibrinogen to fibrin, which fills the space between platelets. Condensation of thrombus is facilitated by retraction of fibrin.

Thus, platelets determine the mechanisms of platelet-vascular hemostasis. In the process of coagulation, platelet membranes are a kind of matrix on which the formation of enzyme-substrate

complexes occurs and the cascade process of serine protease activation. Isolation of thromboplastin by platelets contributes to the activation of the external way of blood clotting.

Coagulation hemostasis. With damage to the arteries and veins, hemostasis occurs not only with the participation of platelets, but also due to clotting of blood and the formation of a coagulation thrombus. A prerequisite for the formation of a thrombus is the interaction of plasma, platelet and tissue factors. Phospholipids of platelet membranes are the place where fixation of procoagulants occurs and their activation.

Blood coagulation is a complex autocatalytic process, in which sequential activation of inactive factors and the formation of serine proteases occur. There are three consecutive stages of coagulation hemostasis: the formation of prothrombinase; Thrombin formation; Formation of fibrin.

Formation of prothrombinase. The formation of prothrombinase takes place along the internal and external pathways.

The internal pathway for the formation of prothrombinase begins with contact activation of factor XII in damage to the vascular wall. This is facilitated by naked collagen filaments and the action of proteases of the damaged endothelium. The phase of contact activation is completed by the formation of active factor XI (factor X1a). Fletcher factors (plasma precalicyrein) and Fitzgerald (high molecular weight kininogen) participate in this process, which accelerate the activation of factor XI and additionally provide the activation of factor XII, as well as zinc ions. Factor X1a on the platelet membrane converts factor IX into factor IXa. Further, an enzyme-substrate complex is formed with the inclusion of factors 1Xa and X, coenzyme of factor VIII and participation of Ca2 + ions. The result of this process is the formation of factor Xa.

Factor VIII is a complex protein consisting of several subunits. The transport factor VIII subunit is the von Willebrand factor (factor W), which provides stability in the circulatory bed of factor VIII and the necessary concentration in the damage zone. Therefore, with a pronounced deficit of factor W, there is a deficiency in the activity of factor VIII.

External pathway of protrombinase formation is realized when the vascular wall is damaged and the interaction of tissue, platelet and plasma factors of hemostasis. When tissue (for example, the vascular wall) is damaged, tissue thromboplastin (factor III), which is a lipoprotein containing phospholipids and possessing protease activity, enters the bloodstream. Cytokines (IL-1, IL-8, FIO), which activate the formation and isolation of factor III from endothelial cells and monocytes, can play a large role in the mechanisms of tissue factor release. Tissue thromboplastin forms a complex with factor VII and Ca2 + ions. This complex activates factor X. The external mechanism provides faster formation of prothrombinase. However, effective hemostasis is possible only with the normal functioning of both mechanisms of protrombinase formation.

There is an additional possibility of activation of factors IX and XI by the complex "factor III-factor VII" (Josso loop), which promotes the formation of thrombin in the internal pathway.

Formation of thrombin. A complex of factors Xa, V, platelet phospholipids (factor III), calcium ions and is a prothrombinase, which splits prothrombin to thrombin. The factor Xa, which is part of the prothrombinase, cleaves a large fragment from the prothrombin molecule and creates an inactive intermediate product, prothrombin 2, which is further cleaved by factor Xa to thrombin that cleaves fibrinogen to fibrin. The resulting thrombin regulates thrombinogenesis, splitting the prothrombin molecule to inactive prothrombin I and thereby preventing the formation of new portions of thrombin. The main function of thrombin is the cleavage of fibrinogen. It also promotes aggregation and platelet release, the biosynthesis of thromboxane A2 activation of factor XIII, etc. In the clinical picture, the multifactorial effect of thrombin on hemostasis is of decisive importance in patients with disseminated intravascular coagulation (thrombinemia).

Formation of fibrin. In the third stage of blood coagulation under the influence of thrombin, fibrinogen is cleaved and converted into soluble and insoluble fibrin. The transformation of fibrinogen into fibrin occurs in three stages.

Stage I - proteolysis of fibrinogen by thrombin; Peptides A and B are cleaved from the amino acid portion of the a and β chains, forming a fibrin monomer.

II stage - polymerization of fibrin monomer and formation of a soluble fibrin polymer sensitive to plasmin.

Stage III - stabilization of soluble fibrin under the influence of factor XIII and the formation of insoluble fibrin, resistant to plasmin.

Factor XIII (transamidase) is synthesized in the liver, circulates in the plasma, and is also contained in platelets, erythrocytes, the vascular wall. In plasma, factor XIII is in the form of an inactive precursor, which is activated by thrombin in the presence of Ca2 + ions. The XI factor stabilizes fibrin by forming covalent cross-links in the fibrin-polymer molecule. After stabilization of fibrin, a red blood clot is formed, consisting of insoluble fibrin and formed elements of blood. Further consolidation of the thrombus occurs due to retraction under the influence of thrombostenin of platelets.

Anticoagulant system of blood. The rate of thrombus formation, its size, the possibility of spontaneous lysis, depends not only on the activity of coagulation factors, but also on the content of natural anticoagulants in the blood and the activity of the fibrinolytic system.

Natural anticoagulants are divided into primary and secondary.

Primary anticoagulants. They are constantly formed in the body and enter the blood, where they interact with the active form of procoagulants and inhibit them. The primary anticoagulants include antithrombin III (AT III), heparin, cofactor II heparin, a2-macroglobulin, protein C, thrombomodulin, protein S, etc.

Antithrombin III (AT III) - α2-globulin with a molecular weight of 58,000, is formed in the liver and endothelial cells. Heparin-sulfated glycosaminoglycan-mucopolysaccharide, with a molecular

weight of 4000 to 40,000, is synthesized in mast cells and basophils of blood. A lot of it is contained in the liver and lungs.

AT III inactivates factors IIa, IXa, Xa, XIa, Xa, XIIIa, stimulating the formation of an enzyme-inhibitory complex with the inclusion of heparin from them. The kinetics of this process depends on the sequence of inclusion in the complex of AT III, heparin and enzyme-coagulant. In sum, heparin increases the activity of AT III approximately 2000 to 3000 times, i.e. Is included as an immediate blood coagulation inhibitor. Heparin, connecting with AT III, changes its conformational structure, with the active center of the latter becoming "more accessible" for thrombin.

The proportion of AT III and heparin is approximately 80% of the total anticoagulant activity of the blood. The complex «AT III - heparin» can be fixed on membranes of endothelial cells, providing thrombore resistance of the vascular wall.

α2-macroglobulin is a glycoprotein that has a nonspecific antiprotease activity. It reversibly binds and transports factors IIa, XIa, XIIa, kallikrein, plasmin, trypsin, chemotripsin and proteases of the acute phase of inflammation. This glycoprotein interacts with thrombin much more slowly than AT III.

Protein C is a vitamin K-dependent protein formed in the liver. Anticoagulant properties show only the active form of protein C (A-PrC). The natural activator of PrS is thrombin. In the body, activation of PP is carried out on the surface of membranes of endotheliocytes with the participation of membrane protein of endothelial cells - thrombomodulin. The proteolytic activity of the "thrombomodulin-PrC" complex is significantly enhanced in the presence of another vitamin K-dependent protein-protein S, phospholipids of the cell membrane of platelets. The active form of protein C inhibits non-enzymatic coagulation factors - Va and VIIIa, by subjecting them to proteolysis.

Thrombomodulin is a protein integrated into the cell membrane of the epithelium. It is found in the endothelium of macro - and microvessels of all organs, except for microvessels of the brain. Thrombomodulin has a great affinity for thrombin and reversibly binds to it, while Ca2 + ions are not required. After the connection with thrombomodulin, the conformational changes take place in the thrombin molecule and the newly formed complex shows the activation properties of PrC in the presence of Ca2 + ions. The rate of this process is induced by thrombin in 20,000 times.

Thrombomodulin promotes the release of tissue plasminogen activator, reduces the activity of the tissue thromboplastin inhibitor (antithromboplastin).

Protein S - glycoprotein, is formed in the liver and endothelium, is contained in granules of platelets. It significantly enhances the anticoagulant effect of A-PrS.

The main function of npS is the optimization of the binding of the active PRC to the surface of the membranes, which catalyzes the proteolytic inactivation of the factors Va and VIIIa. Protein S with the active form of protein C blocks the platelet receptors to the factor Xa. The interaction of Pr, thrombin, thrombomodulin and npS occurs with the participation of the endothelial cell membrane (Figure 18.5). Thus, the thrombin-activated system of PrC-npS, on the one hand, inhibits haemocoagulation, and the other increases the fibrinolytic activity of the blood. Activation of this system is considered as a primary anticoagulant mechanism.

The natural anticoagulants of the external pathway are the lipoprotein-associated coagulation inhibitor (polypeptide), the inhibitor of the external clotting pathway, the apolipoprotein A and protease inhibitor (antithromboplastins), which decrease the activity of factors II and VIIa, the lipid inhibitor is a competitive inhibitor of platelet factor III, the mechanisms of their action are under study.

Secondary anticoagulants. These anticoagulants are formed in the process of blood coagulation and fibrinolysis. These include:

- antithrombin I (fibrin) - sorbs thrombin and factor Xa and turns them into inactive forms;
- antithrombin IV - the product of thrombin prothrombin cleavage, disrupts prothrombin activation by prothrombinase;
- antithrombin VI - degradation products of fibrin, disrupt the polymerization of fibrin monomer, inhibit platelet aggregation, factor Xa, thrombin.

Fibrinolytic system of blood.

Fibrin, formed in the process of blood clotting, undergoes cleavage - fibrinolysis. Central to the system of enzymatic fibrinolysis is the activation of plasminogen with the formation of active plasmin, the main enzyme of the fibrinolytic system. Substances that cause this reaction are called plasminogen activators, they are found in many tissues and body fluids. There are two types of tissue activators of plasminogen (TAP) - tissue (TAP 1) and urokinase (TAP 2). They are a series of new proteases that are synthesized mainly in endothelial cells, and are also formed in the process of microsomal and lysosomal oxidation in all organs, with the exception of the liver. The greatest amount of activator is formed in the uterus, thyroid gland, adrenal glands, lungs, prostate gland. TAP 1 is synthesized in monocytes, macrophages and secreted into the blood in small amounts. In the epithelial cells of the renal tubules, urokinase is formed, which causes the activation of circulating plasminogen and determines 15% of external fibrinolytic activity. Protease of leukocytes possess independent fibrinolytic activity.

Under stress, physical activity, the introduction of some pharmacological drugs (ADH, catecholamines, drugs containing nicotinic acid), the activity of the plasminogen activator in the circulating blood is rapidly increasing. Powerful stimulants of TAP release are vasoactive substances, especially adrenaline, histamine. When TAP 1 is released from tissue damage, it causes local fibrinolysis that does not actually affect the total fibrinolytic activity of the blood.

Fibrinolysis is a protective mechanism that prevents excessive deposition of fibrin and thus maintains normal conditions for microcirculation. Fibrinolytic activity of blood depends not only on the content of plasminogen and its activators, but also on fibrinolysis inhibitors. Inhibitors of fibrinolysis are divided into two groups: anti-activators and antiplasms.

Inhibitors of the activator of plasminogen of the first type are produced by endotheliocytes, hepatocytes and bind TAP. Their production is increased in patients with myocardial infarction, with inflammatory processes. The inhibitor of the plasminogen activator of the second type, formed in endotheliocytes and monocytes and macrophages (including the placenta), inhibits urokinase activity. Large amounts of inhibitor of the activator of plasminogen of the second type are produced by cells of malignant tumors. Anti-activators inhibit the activation of plasminogen, with predominantly local action. In recent years, a certain value has been attached to the inhibitor of

fibrinolysis activated by thrombin (TAFI - thrombin activator fibrinolys inhibitor). It is a protein that, after activation by thrombin, acquires antifibrinolytic activity.

Antiplasms inactivate plasmin and are in abundance in the plasma. These include: a2-macroglobulin, a-1-antitrypsin, complex "AT III-heparin", etc. The most important as a physiological inhibitor of plasmin is the antiplasmin-a-2-glycoprotein, formed in the liver. Antiplasmin for 0.1 sec irreversibly neutralizes the circulating plasmin, and also prevents the binding of plasmin to fibrin and, thus, has an additional antifibrinolytic effect. A2-Macroglobulin inactivates plasmin, which interacts with fibrin.

In addition to fibrinolysis associated with the action of plasmin, formed from plasminogen under the influence of the above activators, the factor XII-kallikrein-dependent fibrinolysis and complement-mediated fibrinolysis are isolated.

Heparin-dependent fibrinolysis. This type of fibrinolysis develops after the formation of complexes, which can include AT III-heparin, thrombin, plasminogen, plasmin, fibrinogen, catecholamines, serotonin, factor XIII, thyroxine. These complexes have a lytic effect on unstable fibrin, inhibit the polymerization of fibrin monomer and stabilize it with factor XIII. It is believed that ε-aminocaproic acid inhibits precisely heparin-dependent fibrinolysis. Proteases released from granules of activated leukocytes, especially neutrophils, proteases of microorganisms and fungi (streptokinase, brynza, ochrase), pancreatic proteases (trypsin, chymotrypsin) have independent fibrinolytic activity. Activation of fibrinolysis is observed with the action of tumor necrosis factor (TNF), as well as under the influence of IL-1.

Complement-mediated fibrinolysis. When the C8 fragment is activated, plasminogen converts to plasmin, the C3a component participates in the lysis of the fibrin clot.

A significant increase in fibrinolytic blood activity is normally compensated by neutralization of plasmin and increased elimination of plasminogen activators. In pathological processes, primary and secondary activation of fibrinolysis is possible.

Mechanisms of thrombophilia. Thrombophilia is a condition characterized by a predisposition to thrombosis. For the development of thrombophilia, vascular damage to the vascular wall (alteration of thrombogenic activity and thrombus resistance of blood vessels), platelet (increased platelet function and thrombocytosis) and plasma mechanisms (increase in active coagulants in blood - hypercoagulation, decrease in anticoagulant blood activity, inhibition of fibrinolysis).

Changes in thrombogenic and thrombo-resistant activity of the vascular wall. In the cellular elements of the vascular wall, substances such as tissue thromboplastin (factor III), fibronectin, von Willebrand factor, thromboxane A2, platelet activating factor and others that form a thrombogenic potential are formed. Some of them initiate thrombinogenesis and fibrin formation, others - adhesion and aggregation of platelets. In physiological conditions, the formation and release of thrombogenic factors in the vascular wall is limited, and when it is damaged or activated by the active substances (adrenaline, histamine, serotonin, bradykinin, interleukin-1, thrombin, etc.), the endothelium significantly increases.

In the mechanism of increasing the thrombogenicity of blood vessels, intramural thrombosis, which develops with microdamages of the endothelium, is of great importance. Various factors are released from the platelets, including the growth factor (factor 4), which causes the proliferation of smooth muscle cells and fibroblasts, their migration to the endothelium, and the enhancement of the secretion of collagen and other connective tissue components that have thrombogenic properties. This mechanism of damaging the vascular wall is most pronounced in diabetes mellitus and atherosclerosis.

Endothelial cells are both producers and effectors of IL-1, IL-6, IL-8, FIO, the growth of their production is noted in sepsis, tumors, inflammation and serves as a nonspecific response to damage to the endothelium. This leads to an increase in the adhesive properties of endothelial cells, inhibition of thrombomodulin activity on the endothelium, and also to an increase in the production of factor III, which leads to the formation of thromboses. In recent years, the importance of the syndrome of antiphospholipid antibodies in the pathogenesis of thromboses and hypercoagulability

is widely discussed. For the first time they were found in patients with systemic lupus erythematosus, who had thrombosis of veins and arteries. At present, anti-phospholipid antibodies in the pathogenesis of IHD have a definite value.

A certain role in damage to the endothelium can also be played by smoking. In a complex mechanism, damage is attributed to a decrease in the production of nitric oxide, an increase in the sensitivity and release of endothelial vasoconstrictors, and a decrease in the angioprotective role of high density lipoproteins due to a decrease in their synthesis in the liver.

Recently, in the damage to the vascular wall, great importance is attached to the disruption of the amino acid exchange of homocysteine - hyperhomocysteinemia, which is often (10-15%) observed in the European population, with the initiation of oxidative stress and associated endothelial damage, and the proliferation of smooth muscle cells of the vessels , Which contributes to the development of atherosclerosis. The risk of damage to the vascular wall during hyperhomocysteinemia is comparable to that of hypercholesterolemia, hypertension, and tobacco smoking.

Along with the thrombogenic properties of the vessels have antithrombogenic properties, or thrombore resistance. In the endothelium and to a lesser degree in other cells of the vascular wall, a number of factors are formed that inhibit blood clotting, activate fibrinolysis, inhibit aggregation and adhesion of platelets. Factors that have anticoagulant activity and are formed mainly in the endothelium include proteins C and S, thrombomodulin, heparin sulfates, etc. It is the glycosaminoglycans that make up a pronounced negative charge of the endothelial wall, which prevents the adhesion of blood cells on the vascular wall. Activation of fibrinolysis occurs with the participation of the vascular activator of plasminogen and protein C, and the inhibition of platelet aggregation - under the influence of prostacyclin, the endothelium relaxation factor, N0. Some proteoglycans also inhibit the aggregation of platelets and their adhesion to endothelium and subendothelium. Increased thrombogenic activity of the vascular wall and a decrease in thrombore resistance provide conditions for thrombosis even with a slight damage to the vessel.

Increase in the functional activity of platelets and thrombocytosis. Increased propensity of platelets to adhesion and aggregation is observed in atherosclerosis, diabetes, hypertension and other diseases. The enhancement of platelet aggregation can be primary, i.e. Associated, for example, with hyperproduction of thromboxane A2, which is observed with insulin-dependent diabetes mellitus, late gestosis of pregnant women, development of malignant tumors, etc.

Hyperglycemia, hyperlipidemia (especially low-density lipoproteins) contribute to an increase in platelet aggregation activity and their sensitivity to aggregation inducers. In insulin-dependent diabetes mellitus, this is due to the presence of glycosylated platelet receptors, which ensures their greater reactivity, including active adhesion to the collagen of the vascular wall. An increase in the blood levels of adrenaline, β-lipoproteins, free fatty acids, factor W is accompanied by a significant increase in aggregation activity of platelets. Deficiency of prostacyclin as the main antiplatelet agent is also characterized by hyperaggregation of platelets.

The increase in the number of platelets above 600 x 10^9 / L, as a rule, causes thrombophilia, thrombocytosis, observed in certain myeloproliferative diseases (Vakeza disease, myelofibrosis), and as a reaction to splenectomy, iron deficiency.

For thrombogenic situations, as a rule, a decrease in the threshold of platelet sensitivity to aggregation inducers, increased spontaneous aggregation of platelets in the bloodstream, a decrease in the lifetime of circulating platelets is characteristic. Plasma increases the level of intra-platelet factors β-thromboglobulin, anti-heparin factor, etc.), indicating the activation of the "release reaction". The use of medicinal inhibitors of platelet receptors for fibrinogen IIb / IIIa is of great importance in situations in which thromboses of arterioles lead to critical conditions, myocardial infarction, etc.

Increase in the content of procoagulants in the blood. In some cases, for example after acute blood loss, an increase in blood clotting is a compensatory reaction. Long and pronounced hypercoagulation creates conditions for thrombosis.

An increase in the activity of plasma procoagulants and coagulation potential alone does not lead to thrombogenesis, but if the vascular wall is damaged, it accelerates and spreads thrombosis. In the mechanism of hypercoagulability in conditions of pathology, the receipt of tissue thromboplastin from the vascular wall into the blood is of great importance. This leads to the formation of prothrombinase and thrombin in amounts exceeding the antithrombin activity of the blood, resulting in increased coagulation potential. In mobilizing activators of blood coagulation from the vascular wall under stress, adrenaline plays a big role. Activation of the sympathetic-adrenal system stimulates the synthesis of fibrinogen, and glucocorticoids - the synthesis of prothrombin, fibrinogen, proaccelerin.

An increase in the activity of procoagulants may be due to the direct action of certain plasma components from them. Hyperlipidemia creates conditions for spontaneous activation of factor XII and acceleration of prothrombinase formation. Hyperlipidemia and thromboplastinemia are noted after intense emotional and physical exertion, so professional athletes are likely to have acute coronary artery thrombosis with a decrease in the thrombore-resistant properties of the vascular wall. In patients with clinical manifestations of atherosclerosis and hypertensive disease, a significant increase in the blood of fibrinogen, prothrombin, factors VIII, XII, etc. occurs. Massive entry into the blood of tissue thromboplastin as a result of extensive tissue damage, hemolysis, intravascular activation of factor XII in septicemia can lead to intravascular coagulation Blood and hemodynamic disorders. Pregnant women from the end of the II - beginning of the III trimester have progressive growth in the plasma of coagulation factors I, II, VII, VIII, IX, XI, XII. By the end of a physiologically occurring pregnancy, their level rises on average to 150-300%; The concentration of fibrinogen is 4-5 g / l.

For dysfibrinogenemia, inherited autosomally recessively, an abnormal synthesis of fibrinogen molecules is characteristic.

Reduction of anticoagulant activity of blood. One of the causes of thrombophilia is a deficiency of natural anticoagulants and, above all, AT III. Disturbance of AT III metabolism can be congenital and acquired. The congenital deficiency is inherited by the autosomal dominant type and manifests itself both in a decrease in the production of AT III and in its affinity for heparin and thrombin. The acquired deficiency of AT III develops in patients with hepatic insufficiency and a predominant decrease in the synthetic function of hepatocytes, including those caused by vitamin A deficiency. The variant of acquired deficiency of AT III is depletion of its depot in patients with chronic renal failure, with nephrotic syndrome, acute venous thrombosis, Syndrome, against a background of intensive heparin therapy. It is possible to bind AT III antibodies.

In atherosclerosis, diabetes, late stages of hypertension, the heparin content in the blood decreases, this is due to the depletion of endogenous resources of heparin as a result of its constant consumption as a coenzyme of lipoprotein lipase. One of the reasons for heparin-resistance may also be a disruption of the interaction of AT III with heparin in patients with systemic lupus erythematosus, Shenlene-Henoch disease. Congenital deficits of PrS and npS are inherited by an autosomal dominant pathway, the incidence in the population is 1: 300. Reduction of the content of FIpS in the blood is described in normal pregnancy, the intake of hormonal contraceptives, thrombosis of the splanchnic veins and is a risk factor for thrombosis and hypercoagulability.

Oppression of fibrinolysis. Factors contributing to thrombosis include oppression of fibrinolysis. Most often, the cause of oppression of fibrinolysis is a metabolic disorder in the vascular wall and a decrease in the secretion of tissue activators of plasminogen (atherosclerosis, hypertension, rheumatoid arthritis). The amount of TAP decreased in patients with myocardial infarction. Fibrinolytic activity decreases with inflammation due to increased endothelium production of the inhibitor of the first type of plasminogen activator. Large amounts of inhibitor of TAP 2 (urokinase) are produced by malignant tumor cells. In pregnancy, as a rule, the production of TAP under the influence of progesterone and placental lactogen decreases.

Excess antiplasms can also lead to a thrombophilic condition. Severe cases of thrombotic disease associated with a genetically determined increase in the production of antiplasms are described. An increase in the number of circulating inhibitors of plasmin and a decrease in fibrinolytic activity is observed in kidney diseases.

A sharp decrease in the fibrinolytic activity of the blood is observed with a deficiency of factor XII, pre-kalikrein, high-molecular kininogen. Factor XII dependent fibrinolysis is disrupted in vasculitis, disseminated by intravascular coagulation, intensive treatment with streptokinase, etc.

Mechanisms of hypocoagulation and bleeding. Hypocoagulation and bleeding are symptoms and complications of many diseases. The most common causes of hemostasis are: thrombocytopenia and thrombocytopathy; Deficiency of plasma procoagulants; Increased anticoagulant blood activity; Hyperfibrinolysis.

Thrombocytopenia and impaired functional activity of platelets. With pronounced thrombocytopenia (less than 40 10^9 / l), the formation of prothrombinase (deficiency of factors III, II) decreases and slows down the stages I and II of blood coagulation. With a decrease in the number of platelets below 20 x 10^9 / l, retraction of the clot, which is carried out with the participation of the platelet factor - thrombostenin, is also disturbed. Disorders of platelet formation in the bone marrow occur in diseases such as B12 and folic deficiency anemia, radiation sickness, tuberculosis, leukemia, and metastasis of tumors in the bone marrow. Congenital thrombocytopenia may accompany chromosomal abnormalities such as trisomy over the 13th, 18th, 21st pairs of chromosomes. Some medications (trimethoprim, methoxazole, cytostatics, estrogens, thiazide diuretics), alcohol cause a decrease in platelet production.

Thrombocytopenia can also develop as a result of increased destruction of platelets during transfusion of old canned blood (with a shelf life of more than 5 days), in a centrifugal pump of the pulmonary circulation apparatus and platelet damage by prosthetic heart valves ("active" surface).

Lysis of platelets during the cytotoxic reaction is associated with the effect of antiplatelet antibodies, primarily IgG (90% of cases). This is observed with immune thrombocytopenic purpura (Verlhof disease), with systemic lupus erythematosus. Antithrombocyte antibodies of a pregnant woman, bypassing the hematoplacental barrier, cause thrombocytopenia in the fetus. Thrombocytopenia due to heteroimmune changes can occur in children during convalescence after acute respiratory viral infections (influenza, adenovirus), cytomegalovirus infection, rubella, measles, chicken pox, sepsis, and after vaccination. Immune mechanisms of thrombocytopenia have definite value in patients receiving sulfonamides, rifampicin, quinidine, and gold preparations. Thrombocytopenia is often found in people with HIV infection. Probably, the combined mechanisms of thrombocytopoiesis disorder caused by IL-2 deficiency and changes in IL-3 activity, immune platelet damage, and the action of medications are likely to be included.

Thrombocytopenia is characteristic of the Shenllein-Genoch syndrome, hemolytic-curum syndrome, and the Moszkowitz disease (thrombotic thrombocytopenic purpura). In these situations, the decrease in the number of circulating platelets is caused by their intensive consumption in the process of microthrombogenesis.

When thrombocytopenia is marked sluggish healing of wounds in the oral cavity, as platelet growth factors are necessary for normal repair of mucosal cells.

Primary thrombocytopathy is due to genetic disorders of the platelet receptor apparatus or deficiencies in the storage pools of granules. In these cases, the intensity of adhesion and aggregation of platelets decreases.

Thrombocytopathy associated with a deficiency of platelet factors (the number of factors III and IV) is manifested by a violation of the release reaction and a decrease in their adhesive and aggregation activity. In this case, even against a normal number of platelets, the time of bleeding from the vessels of the microcirculatory bed increases.

Secondary thrombocytopathy occurs with the use of non-steroidal anti-inflammatory drugs (salicylates, brufen, butazolidine), antidepressants (MAO inhibitors), cardiac glycosides,

adrenoblockers, antibiotics (levomycetin, carbenicillin, large doses of penicillin), thiazide diuretics, antihistamines.

The mechanism of action of the listed drugs is reduced to a decrease in the formation and depletion of storage pools of certain platelet factors.

he rapid depletion of storage pools occurs in platelets of canned blood already within the first 24 hours after its preparation.

Clinical signs of thrombocytopathy are manifested by subcutaneous hemorrhage, gingival (extraction of teeth, use of a rigid toothbrush), nasal, menstrual bleeding.

Deficiency of plasma procoagulants. Deficiency of plasma procoagulants is manifested by the violation of the coagulation unit of blood coagulation and hypocoagulation. Deficiency of plasma procoagulants is observed with hereditary or acquired violations of their biosynthesis, increased consumption (excessive use during the coagulation process, the action of antibodies), and also an increase in the rate of their decay.

Hereditary hypocoagulation occurs in patients with a deficiency of almost all coagulation factors. Hereditary deficiency of plasma procoagulants is quite rare and does not always manifest clinically. This is because in the blood of a healthy person there is a significant excess of each factor. So, for normal hemostasis, only about 30-40% of the prothrombin present in the blood, 5-10% of proconvertin, 25-50% of fibrinogen, etc. are required.

Hereditary deficiency of factors XII, IX, VIII, VII leads mainly to a slowing down of the first stage of blood clotting and a decrease in the formation of prothrombinase, a deficiency of factor II to a slowing down of the second stage of blood coagulation and a decrease in the formation of thrombin.

Hereditary coagulopathies in 90% of cases are associated with deficiency of factors VIII and IX (haemophilia A and B) and von Willebrand disease.

Haemophilia A is noted in the population of one for 10 - 100 thousand men. Some members of families of patients with hemophilia A have now succeeded in detecting an abnormal allele when inheriting fragments of RFLP S associated with the factor VIII gene in the 10th chromosome. This gene often mutates, which explains the appearance of new "sick families". The locus responsible for the synthesis of factor VIII adjoins the loci of color blindness and the enzyme glucose-6-phosphate dehydrogenase. The development of delayed hemorrhage in patients with hemophilia A is only observed with factor VIII deficiency in more than 75% of cases. Transport factor VIII is carried out by the plasma part of factor W. Therefore, in patients with hemophilia A there is a compensatory increase in the level of factor W in plasma, which facilitates the delivery of factor VIII to the matrix of the prothrombinase complex. In patients with haemophilia A (mild and moderate severity - the concentration of factor VIII above 5%) in response to damage to the vascular wall, the release of factors VIII and W from the endothelium is significantly increased, especially after the administration of vasopressin drugs. During surgery, a significant release of factor III in these patients, combined with preoperative preparation (transfusion of cryoprecipitate, blood plasma) to some extent prevent severe blood loss.

In women - conductors of hemophilia A, the deficit of factor VIII is approximately 50% of its normal level in the plasma of healthy individuals. Clinically, such a deficit of the factor can manifest only in operations with severe blood loss and during childbirth.

Hemophilia B (Christmass disease) is a disease caused by factor IX deficiency, the path of inheritance is recessive, linked to the X chromosome. Frequency of occurrence is 1 / (100 - 700 thousand). The hemophilia clinic B is indistinguishable from hemophilia A, and the diagnosis is established using laboratory diagnostics. Approximately 1% of hemophilia B patients also have antibodies inhibiting factor IX in the plasma.

One of the manifestations of hereditary disruption of the synthesis of plasma procoagulants is the formation of abnormal clotting factors, such as factor VIII (hemophilia A), factor IX (hemophilia

B), factors I, II, IX, XIII. By their immune properties, they are similar to normal factors, but functionally inactive.

Factor XIII deficiency refers to rare diseases with an incomplete-rooted type of inheritance, manifested by a violation of the formation of cross-links of fibrin. Rapid lysis of inferior fibrin lining in patients is manifested by slow healing of wounds. Due to the violation of embryo implantation, women experience habitual miscarriages. In newborns from the first days of life, there is a so-called umbilical syndrome, characterized by high bleeding from the umbilical cord and poor

aling of the umbilical wound. Factor XIII, apparently, participates in the mechanisms of spermatogenesis, since men with this deficiency suffer infertility.

Von Willebrand disease is a disease that occurs in persons with a deficiency of factor W, the path of inheritance is autosomal dominant, less often autosomal recessive. Frequency of occurrence 1 / (10 -20 thousand). The latent course of von Willebrand disease is observed in 1% of the population.

The factor W consists of two components - plasma and vascular (antigenic). Plasma factor W is a transport coarse-molecular component of factor VIII, vascular factor W provides adhesion of platelets. Therefore, the value of factor W is reduced to its participation in the mechanisms of platelet-vascular and coagulation hemostasis.

Several types of Willebrand disease are described: type I and type III are caused by a quantitative deficit of unchanged factor W, and IIa and IIb types are associated with the synthesis of abnormal W factor molecules. Clinically, the disease is characterized by the appearance of bleeding immediately after injury, bleeding from the vessels of the microcirculatory bed, the appearance of petechial hemorrhages , Vesicles with hemorrhagic contents in the oral cavity, in women - with hyperspolymenorei.

Acquired hypocoagulation is observed much more often. The reason for the disruption of the coagulation mechanism of hemostasis is a lack of biosynthesis of procoagulants or an increase in their elimination due to disintegration, consumption, and binding. With liver diseases (hepatitis, cirrhosis, toxic lesions), biosynthesis of factors 1, II, V, VII, IX, X, XIII in hepatocytes decreases. Most often, there is a decrease in the activity of factors VII and II. This is one of the reasons for reducing the coagulation potential of blood in patients with liver disease.

In the synthesis of factors II, VII, IX, X, vitamin K is required at the final stage of their formation, when glutamic acid is included in the γ-carboxylation reaction. Therefore, these factors are called vitamin K-dependent and procoagulants. Vitamin K enters the body with food, in the small intestine it is emulsified and absorbed. The source of endogenous provitamin K is the saprophytic bacterial flora of the intestine, it is transported to the liver where it is converted into active vitamin K (epoxide) in the hepatocyte microsome with the participation of epoxidase. Deposited vitamin K in the liver, its reserves are sufficient for the synthesis of vitamin K-dependent procoagulants for 20 to 30 days. Absolute deficiency of vitamin K develops when its intake is insufficient with food, impaired absorption in the intestine in the syndrome of malabsorption (hypo and achiolia, enteropathy), its insufficient formation of intestinal microflora in dysbacteriosis. The relative deficiency of vitamin K occurs when the body's need exceeds its intake.

Physiological deficit of vitamin K is observed in newborns due to insufficient colonization of the intestine with microflora. Under physiological conditions, the biosynthesis and decomposition of clotting factors are in a state of dynamic equilibrium. In many pathological processes, this equilibrium is disrupted and, in particular, the decay prevails over the synthesis, which leads to a decrease in the activity of procoagulants and hypocoagulation. Blood clotting is reduced, hemorrhagic complications are often observed.

In canned blood, the number of factors V and VII is sharply reduced, since they are the shortest-lived (the half-life of factor VII fluctuates from 2 to 6 hours).

To the majority of plasma procoagulants, antibodies can be produced, in their structure it is usually IgG, which inhibit clotting factors.

Deficiency of factor V is observed in patients with chronic myelogenous leukemia in the presence of the Philadelphia chromosome, as well as in patients with lymphoblastic leukemia.

There are patients with acquired forms of Willebrand disease, usually of an autoimmune nature.

Increase in anticoagulant activity of blood. This condition arises not only because of deficiency of procoagulants, but also in excess of anticoagulants - antithrombin III, heparin.

An increase in the blood of endogenous heparin is observed with collagenoses, leukemias, anaphylactic shock, with thbin formation inhibited and blood clot formation slowing down.

enous hypergeparinemia is associated with an overdose of heparin in the treatment of thromboembolic complications, operations with prolonged extracorporeal circulation. In this case, all stages of blood coagulation are inhibited and hemorrhagic syndrome develops.

Increased activity of AT III is observed in patients with cholestasis (vitamin A deficiency) receiving anticoagulants of indirect action (imbalance between the synthesis of vitamin K-dependent procoagulants and AT III), in women suffering from menorrhagia.

There are primary and secondary hyperfibrinolysis.

Primary hyperfibrinolysis is observed with a massive intake of tissue activators of plasminogen into the bloodstream and a sharp decrease in the formation of antiplasms. The increase in the formation of TAP is noted in cases of progression of the tumor process and severe hepatic insufficiency. In the period of menstrual blood loss, with burns, stress, prescription of drugs of nicotinic acid, the release of TAP also increases. Enzymes of bacterial origin have the ability to activate fibrinolysis. Reduction of the formation of antiplasms and increased fibrinolytic activity often occur in patients with liver damage. They have a pronounced tendency to bleeding, and this is also noted in the genetic defect of production (x2-antiplasmin (Miasato disease).) Enhanced lysis of fibrin can be noted with factor XIII deficiency due to a disruption in the formation of fibrin polymer.

Secondary hyperfibrinolysis is an increase in fibrinolytic activity of blood in response to an increase in fibrin formation, develops against the background of DIC syndrome. The violation of hemostasis in hyperfibrinolysis is due to the dissolution of fibrin and the inability to form a coagulation thrombus. In addition, PDF have an inhibitory effect on platelet aggregation and all stages of blood clotting.

Syndrome of disseminated intravascular coagulation (DIC-syndrome).

DIC-syndrome is characterized by a generalized activation of the system of hemostasis and fibrinolysis, in which there is a mismatch in the regulation of the aggressive state of the blood.

The most common DIC syndrome is a complication of the following diseases:

- shocks of any genesis (in 90 - 100% of cases);
- septic states (in 70% of cases);
- bacteremia and viremia (in 30% of cases);
- tumors, primarily leukemia;
- thromboembolism of the pulmonary artery;
- burns;
- Long crush syndrome;
- obstetric pathology (premature detachment and placenta previa, severe late gestosis of pregnant women, manual removal of the placenta, cesarean section, bleeding);
- Acute intravascular hemolysis and cytolysis (hemorrhagic fevers, malaria, transfusion of incompatible blood, action of snake and fungal poisons);

- operations on the parenchymal organs (liver, spleen, prostate, lung), accompanied by severe blood loss;
- Vascular endoprosthetics, operations on the valvular heart apparatus;
- use of the device of artificial circulation;
- transplantation of organs and tissues.

Mechanisms of DIC-syndrome. At the heart of the DIC syndrome lie: marked activation of the coagulation and thrombocyte links of hemostasis with the addition of a secondary massive endothelial damage. The parallel launch of these mechanisms, each of which is capable of enhancing the other, determines the rapid formation in the vascular bed of active forms of coagulants. The main ways of implementing these mechanisms are as follows:

External activation mechanism is carried out with a massive intake of factor III in patients with extensive burns, decay of tumors, embolism with amniotic fluid, premature placental abruption, with a dead fetus syndrome. Expressed amounts of factor III are released in massive cytolysis, which is caused by death of leukocytes (sepsis, cytostatic therapy), or erythrocytes (crises

hemolytic anemia). The central role in the activation of coagulation in sepsis, inflammation, autoimmune processes is given to the action of cytokines IL-1 and IL-6.

The internal mechanism of activation is observed in the primary diffuse lesion of the vascular wall and the activation of factor XII under the influence of endotoxins. This is observed in sepsis, rickettsial, viral, bacterial infections, damage to the endothelium by immune complexes. The pronounced activation of factor XII leads to simultaneous stimulation of the coagulation and fibrinolysis system, and, consequently, to a multidirectional effect on hemostasis in general. The cytokines (IL-1) have a significant effect on the mechanism of activation of the internal pathway.

Direct activation of factors by proteolytic enzymes, including trypsin in acute pancreatitis (activates factor X and thrombin) by the products of cell death, by toxins of microorganisms.

The primary activation of platelets occurs with tropical malaria, the impact on platelets of soluble complexes of AG-AT in the case of the Shenlein-Genoch syndrome. With pronounced damage to the endothelium, initiation of intravascular aggregation of platelets (contact with collagen and other aggregation activators) is noted, which is observed, for example, in meningococcal sepsis.

In the process of aggregation, a large amount of factor III is released from the perishing platelets, which supports haemocoagulation along the external pathway.

Damage to the endothelium is initiated by immune complexes that activate the cascade of the complement system. The components of C3a and especially C5a increase the formation of free oxygen radicals by activating neutrophils and isolating IL-1, FIO (tumor necrosis factor) from monocytes. Activated neutrophils release serineelastase, which directly damages the endothelium. The most demonstrative are these lesions in sepsis. Damage to the endothelium is possible due to "osmotic impact" in hyperglycemia.

In the clinical picture of ICE, these mechanisms, as a rule, are combined with each other. According to the nature of the flow, acute and chronic DVS-syndrome are isolated. Mortality
with the development of acute DIC syndrome is 30 - 50%.

The process is of a phasic character and always begins with hypercoagulation, which activates the processes of fibrinolysis.

Stage I - hypercoagulable - lasting an average of 15 - 20 minutes. With a rapid flow of DIC-syndrome, it can dramatically decrease. Intravascular coagulation is accompanied by the consumption of coagulation factors and anticoagulants. The resulting thrombi loose, circulating microthrombi represent emboli and, consequently, clog small vessels, disrupting microcirculation in organs and tissues. The leading symptoms in the clinical picture are: cold extremities, severe pallor of the skin,

dyspnea with an inspiratory component, which determines the development of severe tissue hypoxia and metabolic acidosis.

It should be noted that the microthrombi formed in the DIC syndrome have a loose gel-like consistency and are very different in structure from classical blood clots formed in large vessels.

II stage - consumption coagulopathy. Isolate stage IIa, characterized by depletion of clotting factors due to their consumption without excessive activation of fibrinolysis. Stage IIb is characterized by progressive activation of fibrinolysis in combination with increasing hypocoagulation. Activation of fibrinolysis has an adaptive value, since it promotes the partial release of microcirculation from microthrombi and the elimination of tissue ischemia. The plasma reduces the number of platelets, gradually reducing the concentration of fibrinogen. Clinically, this stage is characterized by the appearance of bleeding in the areas of damage (surgical wound, uterine cavity, injection site).

Stage III - hypocoagulation - is characterized by the depletion of all coagulation factors and anticoagulants, expressed by hypofibrinogenemia, thrombocytopenia, as well as abnormal fibrinolytic activity (secondary hyperfibrinolysis). At the same time there is fibrinolysis and fibrinogenolysis, which leads to an increase in the tens and hundreds of times the CDEF in the blood.

Activation of the kallikrein-kinin system of plasma, caused by the presence of activated forms of the factor of HNa, leads to an increase in the permeability of the vascular wall and a decrease in tone. Clinical signs of the stage are progressive bleeding in the areas of damage and previously intact tissues (mucous membranes of the eyes, gastrointestinal tract, genitourinary system, respiratory tract).

IV stage is a stage of outcomes or a stage of residual manifestations of vascular blockade by microthrombi.

When pharmacological correction of disorders in the system of hemostasis in patients with DIC syndrome should take into account the phase nature of its development and the transition from intravascular coagulation to bleeding.

DIC-syndrome can be one of the reasons for the development of increasing multi-organ insolvency, characterized by the development of acute renal failure, hemolytic-uremic syndrome, respiratory distress syndrome, acute adrenal insufficiency

Chronic DIC-syndrome is often found in patients with a tumor process at stages I-IV of its development, chroniosepsis, at the initial stage of renal failure, in pneumonia, influenza and other acute respiratory viral infections.

The process is characterized by prolonged local hypercoagulability and phlebotrombosis in the veins of the lower extremities, less often in the veins of the pelvis and upper extremities (Tussaud's syndrome). The metastasis of dense tumors in 75% of cases is accompanied by migrating phlebothrombosis. Chronic DVS-syndrome can develop in patients with malignant lung tumors, ovaries, mammary carcinoma, prostate carcinoma, disseminated neuroblastoma, metastatic gastric adenocarcinoma, and colon carcinoma. For a clinician, the appearance of signs of persistent phlebotrombosis against the background of normal somatic status and consistency of the venous bed should always serve as a basis for examining the patient and excluding oncological pathology.

With chronic hepatic insufficiency, there is an internal combustion engine with severe hypocoagulation. Development of chronic DVS-syndrome is possible with microthromboskulitis (hemolytic syndrome, thrombotic thrombocytopenic purpura).

Hemolytic-uremic syndrome (Gasser's syndrome) is noted in viral, bacterial infections in children and women who gave birth. Thrombotic thrombocytopenic purpura (Moshkovitsa's disease) actually repeats the pattern of hemolytic-uremic syndrome: fever, hemorrhagic syndrome, acute renal failure, microangiopathic hemolytic anemia. Intravascular coagulation is noted in all organs.

With Shenlen-Henoch disease, the development of DIC syndrome is due to the formation of generalized microthrombovasculitis, which is based on the damage of microvessels by circulating immune complexes and activated components of the complement system. The factor that induces DIC

syndrome in hypertensive disease is most likely damage to endotheliocyte membranes in case of hemodynamic stress.

Micro- or macroangiopathy in diabetic patients is a condition for the development of chronic DIC syndrome. This is promoted by hypercoagulation in combination with hypophybrinolysis and high reactivity of platelets.

A definite value in the pathogenesis of DIC syndrome has a long-term localized intravascular coagulation of blood in various organs, which, as a rule, are damaged by the inflammatory process. This is especially true for glomerulonephritis, acute pneumonia, some diffuse lesions of the liver parenchyma, metroendometritis, salpingo-oophoritis. In the pathogenesis of these conditions, the stage of hypercoagulability of different duration and severity is noted, which is determined by the degree of tissue damage and subsequent chronic release of tissue thromboplastin, as well as chronic damage to the endothelium by immune complexes. The vessels of the microcirculatory bed of these organs are gradually filled with microthrombi, which contributes to depletion of the coagulation potential and activation of fibrinolysis with the development of hypocoagulation in the future. The possibility of developing the DIC syndrome when circulating a significant amount of streptococci in the bloodstream that can enter the systemic circulation from the microvessels of the dentoalveolar system during dental interventions (treatment of caries, etc.) has been noted. Streptococci cause intravascular aggregation of platelets, contribute to the formation and "dispatch" of microthrombi,

including microvessels of the myocardium. In patients, there were cases of myocardial infarction and even development of septic shock.

The examination of patients with changes in the hemostasis system begins with the determination of the number of platelets as direct participants in the process of thrombus formation. For a more detailed evaluation of the hemostasis system, coagulation tests (clotting time, bleeding time, recalcification time, kaolin time, prothrombin index, thrombin time, plasma tolerance to heparin, free heparin, AT III, plasma fibrinogen, fibrinolytic activity, paracoagulation tests) and coagulation tests are used. The study of adhesive and aggregation activity of platelets.

Embolism

Embolism is a typical pathological process caused by the presence and circulation in the blood or lymph of particles not found there under normal conditions, often causing occlusion (blockage) of the vessel with subsequent violation of local blood supply.

As emboli, 99% of all embolisms are clots of blood coagulated inside the blood vessels, that is, clots. Embolism, as well as thrombosis, is an important reason for reducing the cross-sectional area of the vessel, and consequently, the volume velocity of blood flow and perfusion of the blood vessel. Typically, embolism occurs in the arteries as a result of the transfer of emboli along the course of the blood flow. However, embolism of the veins is also possible - if a large embolus gets stuck in the valve area or, moving against the blood flow under the influence of gravity, falls into a narrow section of the vein (retrograde embolism).

Classification of embolism

1. By origin of the embolus:

- exogenous - air, gas, medicamentous embolism, foreign bodies;
- endogenous - thromboembolism (detached part of thrombus), fatty (with trauma, fractures of tubular bones), tumor masses, amniotic fluid, bacterial, solid particles (tissues, microbes, parasites, foreign bodies);

2. Localization:

- a small circle of blood circulation,
- a large circle of blood circulation,
- portal vein.

3. On the mechanism of development: - orthograde - according to blood flow;

- retrograde - against current under the influence of gravity, develops in large venous trunks

with a slowing of blood flow and a decrease in the sucking action of the chest;

- Paradoxical - due to the presence of defects of the interatrial or interventricular septum and other heart defects with the right-left shunt, emboli are able to pass the branches of the pulmonary artery and find themselves in a large circle without getting stuck in the small capillaries;

Air embolism arises from the ingress of air into the vascular system from the environment. Causes of air embolism can be damage to large veins of the neck, chest, sinuses of the dura mater, neurosurgical operations with opening of venous sinuses, artificial circulation, medical and diagnostic puncture of the lungs, laparoscopic operations, improperly conducted intravenous injections, etc.

Air can get into the vessel (most often in a vein or venous sinus) under two indispensable conditions: if there is a message of the vessel with an air source and excess air pressure over intravascular pressure. The development of air embolism is facilitated by a number of concomitant circumstances. So, this embolism often develops in conditions of hypovolemia. When hypovolemia in the venous section of the vascular bed, a negative pressure is created in relation to the surrounding atmosphere, because with a lack of venous return the right atrium sucks blood from the venous vessels. The second circumstance, facilitating the emergence of air embolism, is the deep breaths that makes the patient. A sharp discharge, created at this moment inside the chest, sucks air into the gaping venous vessels, wherever they are.

Gas embolism is associated with the release in the blood of bubbles of gases (nitrogen and helium) soluble in it with a rapid transition from high atmospheric pressure to normal or from normal to low. Such a situation can arise when sudden decompression, for example, with the rapid rise of a diver from a considerable depth. One of the variants of gas embolism is the formation of gas bubbles during blood transfusion using methods of rapid heating of blood to body temperature. The solubility of gas in the blood with increasing its temperature by more than 30 ° decreases, and gas bubbles can enter the bloodstream, the bubbles seem to boil in the bloodstream and clog the blood vessels of the microcirculation. Gas embolism is also dangerous because nitrogen bubbles activate the fibrin system and thrombocytes, provoking thrombosis.

A rare variety is the embolism of putrefactive gases in gangrene.

Microbial embolism occurs when septicopyemia, when the blood flow is a large number of microorganisms. Microbial embolism can be the cause of the development of metastatic abscesses.

Parasitic embolism occurs in helminthiases. So with ascariasis, embolism of the vessels of the lungs is possible. In countries with a hot climate, embolism of lymphatic vessels with filaria occurs, which leads to a violation of lymphatic drainage in the limbs and the development of "elephant disease".

Fat embolism occurs when the vessels are clogged with endogenous lipoprotein particles, chylomicron aggregation products or exogenous fat emulsions and liposomes. Endogenous true fat embolism is observed in type 1 hyperlipoproteinemia, when, due to a defect in lipoprotein lipase, chylomicrons are not cleaved by the lungs and persist in the plasma. The most severe form - the fat-embolic syndrome has a complex pathogenesis and occurs not only from the dissemination of fat tissue elements after injuries of bones and subcutaneous fat, but also from the fusion of chylomicrons. With a true fat embolism, there is a high level of free fatty acids in the blood that have an arrhythmogenic effect, and disturbances in the heart rhythm promote intracardiac thrombosis.

Fat embolism can be accompanied by a unique combination of pulmonary embolism and focal cerebral ischemia due to the passage of chylomicrons and small fat emboli through capillaries:

Tissue embolism is divided into amniotic, tumor and adipocytic embolism.

Embolism with amniotic fluid leads to clogging of pulmonary vessels by conglomerates of cells suspended in the amniotic fluid and thromboembols formed by the procoagulants contained in it.

Tumor embolism is a complex process of hematogenous and lymphogenic metastasis of malignant neoplasms. Tumor cells form in the bloodstream conglomerates with platelets due to the production of mucins and adhesive surface proteins. Activated platelets release growth factors that

help the proliferation of tumor cells. Tumor emboli are spread according to laws different from the classical rules of embolism. Due to specific cytoadhesive receptor interactions, tumor emboli can be fixed in the vessels of certain organs and tissues. So, tumors practically never metastasize into skeletal muscles, spleen. Metastases of many tumors have specific addresses, that is, metastasize only to certain organs.

Tissue (in particular adipocytic) embolism can be the result of injuries, when the particles of the crushed tissues fall and the lumen of the damaged vessels.

Embolism of foreign bodies is quite rare and occurs when injuries or medical invasive procedures.

A variety of endogenous emboli - thromboembolism - arises from the clogging of blood vessels with torn clots or their particles. Thromboembolism is a consequence of thrombosis or thrombophlebitis of various parts of the venous system of the body. One of the most severe is PE, which occurs with phlebotrombosis of central and peripheral vessels, it is promoted by obesity and hypokinesia, varicose veins, prolonged immobilization, cancer, septic lesions, trauma.

Embolism of the great circle of blood circulation.

Embolii BKK. The source of emboli are pathological processes (thromboendocarditis, myocardial infarction, ulceration of atherosclerotic plaques) in pulmonary veins, left cavities of the

heart, aorta, and arteries of a large circle. These embolisms are accompanied by serious circulatory disorders, up to the development of foci of necrosis in the organ, whose vessel is clogged.

Embolism of the small circle of blood circulation

Embolism of the ICC is the result of skidding of emboli from the right side of the heart and veins of a large circle. This type of embolism is characterized by the suddenness of the onset, the rapidity of the growth of extremely severe clinical manifestations.

A piece of blood clot, detached from the wall of a large circle of venous vessel, comes with a blood flow through the hollow veins into the right atrium, the ventricle and from there into the pulmonary artery. In the pulmonary artery, the detached pieces of the parietal thrombi of the right heart also fall. Embolus may linger either in the trunk of the pulmonary artery, or in its branches, or in the pulmonary capillaries. In the right lung there was a heart attack.

Embolism of the portal vein system.

Embolism of the portal vein is formed during pathological processes in the intestinal veins (HES, OCN and HCN, etc.). Embolism of the portal vein is a relatively rare but life-threatening phenomenon that leads to the development of congestive bowel congestion, resulting in up to 90% of the blood accumulating in the abdominal cavity. This leads to a disorder of hemodynamics and death.

Effects of embolism.

Depending on the site of localization, embolism can lead to ischemia (see below) in arterial vessels or to venous hyperemia (see above) - with venous embolism.

Outcomes of embolism.

Systemic thromboembolism of blood vessels of the great circle of blood circulation is accompanied by the development of infarctions of internal organs, ischemic strokes, limb ischemia and violation of the function of the corresponding organs and systems.

The most formidable and dangerous consequence of PE that is a threatened condition for the life of the patient.

INFLAMMATION

Inflammation is general typical pathological process of local character. It includes both local damage of tissues and the local protective inflammatory reaction which are response to this damage.

The inflammatory reaction - it emerged in the course of evolution, the reaction of living tissue to local injury. It consists of a complex incremental changes in microcirculatory blood system and connective tissue and is aimed ultimately at eliminating or isolation of the damaging agent, and so on. Well. repair or replacement of tissue damaging.

Inflammation (inflammatio from Latin in-flammare - igniting) - formed in the evolution of the body's response to local injury, characterized by the phenomenon of alteration, disorders of the microcirculation with exudation and emigration and proliferation, aimed at the localization, the destruction and removal of the damaging agent, as well as to restore (or substitution) they damaged tissues.

Alteration, microcirculation disorders (with exudation and emigration) and proliferation are the main components or internal cardinal symptoms (phenomena) inflammation. In addition, the focus of inflammation is characterized by five external (clinical) cardinal signs: redness (rubor), swelling (tumor), an increase in temperature, or heat (calor), tenderness, or pain (dolor), and dysfunction (functio laesa). These features are particularly well defined as the inflammatory focus is on the outer covering.

Along with the local inflammation can also show general signs, the severity of which depends on the intensity and prevalence of process. Common symptoms include fever inflammation reaction hematopoietic tissue with development of leukocytosis, elevated erythrocyte sedimentation rate, accelerated metabolism, altered immune reactivity, effects of intoxication.

Inflammation is one of the most common types of pathological processes. At the same time it is an important protective-adaptive reaction, evolutionarily formed as a way to save the cost of the whole organism part of the damage. With the help of inflammation provided localization and elimination of the inflammatory agent (flogogen - from the Latin phlogosis -. Inflammation inflammatio synonymous with the term), and (or) damaged tissue under his influence.

GENERAL THEORY OF INFLAMMATION

As the disease process that underlies most human diseases, inflammation is the central problem of pathology throughout the history of the doctrine of the disease. The formation of ideas about the nature of the inflammation has long been closely associated with the development of views on the nature of the disease.

In the experimental period, the pathology in the early stages of inflammation dominated by the theory of R. Virchow (1858) and U. Cohnheim (1885). According to the cell (the attraction, nutritional) theory R. Virchow inflammation is in violation of vital activity of cellular elements in response to stimulation, development of degenerative changes, consisting in the appearance of protein in the cells and clumps of grain, attraction (Attraction) nutritional (nutritional) of material from the liquid part of blood, occurs as a result of cloudy swelling of cytoplasm, characteristic of inflammation.

In the vascular theory U. Cohnheim inflammation is characterized by disorders of blood circulation, leading to exudation and emigration and causes the next cell (degenerative) changes. However, it was later revealed inflammation is characterized by the simultaneous development and the close relationship of vascular and tissue phenomena. U. Cohnheim first described in detail the totality of the changes of vascular tone and blood flow to the exudation and emigration. A particularly large contribution to the study of inflammation brought Mechnikov (1892). It marked the beginning of the comparative pathology of inflammation, the theory of cellular and humoral immunity, the doctrine of phagocytosis and formulated biological (phagocytic) theory of inflammation. According to this main and central element of the inflammatory process is the absorption of phagocytes foreign particles, including bacteria.

Having analyzed the inflammatory response in different species of animals at different stages of evolutionary development, Mechnikov demonstrated its sophistication in the phylogeny. In the

early stages of phylogeny (from the simplest single-celled organisms) protection from foreign material carried by phagocytosis. At the same time, and in the simplest organisms there are some phenomena of alteration. In multicellular organisms, non-vascular, inflammation appears congestion around the injury site amoeboid phagocytic cells (amebocyte). In higher invertebrates inflammation expressed accumulation at the injury site of blood cells - limfogematotsitov. Despite the presence in them of the circulatory system (open type), vascular reactions characteristic of vertebrates, do not occur. However, at this stage evolutionary phenomena detected proliferation. In vertebrates and human inflammatory response it is much more complicated due to vascular events with exudation and emigration, the participation of the nervous system.

The results of the comparative-pathological studies showing the involvement of more and more complex new protective and adaptive phenomena as the complexity of the inflammatory process, allowed Mechnikov show the importance of inflammation as a protective and adaptive reactions of the whole organism. Mechnikov for the first time established a link with inflammation immunity, in which phagocytosis mechanism also plays a significant role.

In the first half of this century, the doctrine of the inflammation was developed in connection with the emergence of biophysical and biochemical methods. Results diverse physico-chemical studies of the inflammatory focus G. Shade allowed (1923) propose physical-chemical or molecular pathological inflammation hypothesis, according to which leading in the pathogenesis of this process is local metabolic disorder that leads to the development of acidosis and increase the osmotic pressure in tissue lying, in turn, based on circulatory disorders and cellular events during inflammation. However, it was soon shown that physicochemical changes characteristic of an inflammatory focus, found already developed in the course of the inflammatory response and consequently may not be a trigger vascular and cellular phenomena. In some types of inflammation (allergic) acidosis does not develop or is weak.

Since the beginning of this century, when it was established part of the nervous system in the pathogenesis of inflammation, any hypothesis, giving to the primary role of the nervous factor - reflex mechanisms, disruption of trophic function of the nervous system. Thus, vasomotor (neuro-vascular) theory G. Ricker (1924) in the event of the primary disorder is an inflammation of the nerves of vasomotor function. Depending on the degree of irritation, and therefore, developing vascular response develops a relationship between tissue and blood, which leads to the appearance of inflammatory hyperemia and stasis and, therefore, determines the intensity and character of metabolic disorders. However, the totality of the inflammatory phenomena can not be explained only by the reaction vessels of the microvasculature.

D.E. Alpern (1959) paid special attention to the issue of unity in the local and general inflammation and the role of reactivity in the development of this process. He emphasized the essence of inflammation as a common reaction of the organism to the action of the harmful agent. They justified the neuro-reflex scheme of pathogenesis of inflammation, according to which a variety of vascular tissue reactions are regulated by neural and humoral (mainly the pituitary-adrenal) systems.

Etiology of inflammation

It causes inflammation of origin:

1. Exogenous
2. Endogenous

The causes of inflammation are nature

1. Physical
2. Chemical
3. Mechanical

4. Biological
5. Social environmental factors

The cause of inflammation may be any factor that can cause tissue damage – flogogen.

Conditions:

1) The strength and duration of action of the stimulus
2) Place of action (vascular availability)
3) The presence of local tissue damage or a certain number of micro-organisms caught in the fabric
4) Status of individual reactivity (power factor, sensitization to the damaging factor, white blood cell count, age, basal metabolism, etc.).
5) Status of the endocrine and nervous systems (stress, anesthesia), the state of immunity

More common inflammation caused by exogenous agents. In turn, the external flogogen in nature may be biological (mostly infectious - bacteria, Rickettsia, viruses, fungi, animal parasites), physical (mechanical, thermal, radiation energy), chemical (acids, alkalis, chemical warfare agents, turpentine, croton and mustard oil, and so on. Internal causes inflammation often are tissue necrosis, hematoma formed stones, salt deposits, immune complexes, and others. As a rule, it is easy to trace the connection between the emergence of endogenous cause's inflammation and the action on the body of exogenous factors.

Because the most common cause of inflammation are infectious agents, it is divided according to the etiology of infectious (septic) and non-infectious (aseptic).

Inflammation has three stages:

I. Alteration;

II. Changes of microcirculation with exudation and emigration of leukocytes; III. Proliferation.

Pathogenesis of inflammation

The pathogenesis of inflammation is a complex combination of neural, and humoral effector mechanisms that underlie a large number of inflammatory phenomena constituting, in turn, effects an alteration, with microcirculation disorders exudation and emigration and proliferation.

The role of tissue damage in inflammation

Alteration (alteratio from Latin alterare - change), or degeneration - tissue damage, disruption in her power (trophism) and metabolism, its structure and functions. There are primary and secondary alteration. The primary alteration is a result of the damaging effects of the inflammatory agent, so its severity, ceteris paribus (reactivity, localization) depends on flogogen properties. Strictly speaking, the primary alteration is not a component of inflammation, because inflammation is a reaction to the damage caused by flogogen, primary alteration. At the same time almost the primary and secondary alterative phenomena difficult to be separated from each other.

Secondary alteration is a consequence of the impact on the connective tissue, and blood microvessels of the released extracellular lysosomal enzymes and reactive oxygen metabolites. They are the source of immigrants and activated circulating phagocytes, partly - resident cells. When inflammation in animals with pre-induced leukopenia alteration is weak. A role in the alterations may also play a lytic complex C5-C9, which is formed by the activation of complement plasma and tissue fluid.

Thus, secondary alteration is not directly dependent on inflammatory agent, for its development in the future is not necessary in the presence flogogen hearth. It is a reaction to already beginning to cause harmful damage. This is an integral part of the inflammatory process. Moreover, it is quite appropriate and necessary component of inflammation as a protective and adaptive reactions. Additional counter damage is aimed at speedy demarcation (localization) flogogen and (or) damaged

by its impact on the fabric of the whole organism. Achieved at the cost of damage and other important protective effects: more pronounced microbicidal and lytic effect of lysosomal enzymes and active oxygen metabolites since it occurs not only in the phagocytes, but extracellularly; involvement of other inflammatory mediators and cells, enhanced exudation, emigration and phagocytosis. The result is a more rapid completion of the inflammatory process. It is clear that the alteration may be appropriate only in certain limits. For example, when an

imbalance in the system lysosomal proteinases - the excess of inhibitors arise from alteration predominant symptoms necrosis.

Alterative effects include inflammation of the tissue at the breakdown and enhanced metabolism ("exchange of fire"), leading to a series of physical and chemical changes in the inflammatory tissue - accumulation of acidic foods (acidosis or - hyperionia H +), increase in osmotic pressure (osmotic hypertension, or hyperospheresia), increase in colloid osmotic or oncotic pressure (hyperoncia).

Depending on the strength of the damaging agent, the intensity and localization of inflammation morphological manifestations of alteration vary widely, from subtle structural and functional changes to the complete destruction (necrobiosis) and death (necrosis) of tissue and cells. Observed cloudy swelling of the cytoplasm of cells, the phenomenon of protein, fat and other types of dystrophy. Dramatically increases the permeability of cell membranes and cell organelles. Changes in subcellular structures relate primarily to the mitochondria, lysosomes, ribosomes, the endoplasmic reticulum. Mitochondria swell or shrink, Kristen them are destroyed. Increased permeability of the lysosomal membranes and damage accompanied by the release of a variety of enzymes that play a role in the destruction of subcellular structures. Change the shape and size of the tanks of the endoplasmic reticulum, cytoplasmic vesicles appear, concentric patterns, etc.. There have been marginal arrangement of chromatin, nuclear membrane damage. The stroma observed mucoid and fibrinoid swelling up to fibrinoid necrosis, dissolution of collagen and elastin fibers.

Increased metabolism in inflammation occurs mainly at the expense of carbohydrates. Initially their enhanced oxidation and glycolysis. This is based on the activation of the respective tissue enzymes. Visibly increases oxygen consumption inflamed tissue. With the accumulation of leukocytes in the outbreak, lysosomal enzymes which break down carbohydrates mainly anaerobically and damage and reduce the number of mitochondria in the course alteration phenomenon of oxidation considerably weakened, and glycolysis - grow. Accordingly, the breakdown of carbohydrates does not always reach the end products - carbon dioxide and water. Respiratory rate decreases. The tissue accumulate oxidized carbohydrate metabolism products - milk and tricarboxylic acids.

Furthermore, due to disturbances of fat metabolism, protein and nucleic acid in the disintegration of the hearth increases fatty acid content, ketone bodies, polypeptides, amino acids, nucleotides (ATP, adenylic acid), nucleosides (adenosine). As a result, develops acidosis. Initially, he compensated tissue buffer systems and rapid blood - and lymph flow. With the depletion of buffer systems and slow blood circulation and lymph flow acidosis increases and becomes uncompensated. The worse the inflammatory process, the more marked acidosis. Acidosis is of some importance in the development of inflammatory phenomena, such as increase in vascular permeability. It creates favorable conditions for the realization of the destructive effects of lysosomal enzymes, such as glycosidases cleaving carbohydrate components of the connective tissue matrix.

Physico-chemical changes in the site of inflammation.

1. Kº - Hyperion (damage and cell death).
2. N ° - Hyperion (acidosis) - oxidized, anaerobic glycolysis. The collapse of the substances under the influence of ALF.
3. Hyperosmia - (↑ osmotic pressure) → disintegration of cells, fibers, compounds (ALF).

4. Hyperoncia (↑ oncotic pressure); Acidosis → ↑ hydrophilic colloids + protein breakdown (under the influence of ALF) + output of albumin from the blood through the vascular wall.
5. Hyperthermia - local heat: in the center: separation of tissue respiration and oxidative phosphorylation; on the periphery: hyperemia (↑oxidation processes → ↑ heat + hot inflow of arterial blood from the internal organs).

Along with H + - Hyperion, increases in the source and content of other ions - potassium, sodium, calcium. This is due to the destruction of cells and enhanced dissociation of salts in an acidic environment. Due to the advanced increase of extracellular potassium is disturbed ratio of potassium and calcium ions (disionia). At the same time increases the molecular concentration,

cause in the process of tissue decay and enhanced metabolic cleavage of larger molecules to many smaller ones. Due to the increase of ionic and molecular concentration develops hyperospheresia. For example, if the rate of depression in the interstitial fluid is - 0.62 °, ie, the osmotic pressure of 8 bar, then at a purulent inflammation of - respectively - 0.80 ° and 19 atm.

As a result of physical and chemical changes in the inflamed tissue, break down proteins into polypeptides and amino acids with an increase in the concentration of the latter is an increase in dispersion of colloids, their ability to attract and retain water. Develops hyperoncia. Changes osmotic and oncotic pressure is an important factor exudation and therefore the inflammatory edema.

Mediators of inflammation

During the primary and secondary alterations released large amounts of various inflammatory mediators and modulators.

Under mediators (intermediaries) inflammation understand biologically active substances responsible for the emergence or maintenance of those or other inflammatory phenomena such as increased vascular permeability, immigration and so on. D. It is the same substance that in a normal functioning of the body to form in various organs and tissues at physiological concentrations, are responsible for the regulation of cellular functions, tissue level. When inflammation, releasing (due to cell activation and liquids) in large quantities, they acquire new quality - mediators of inflammation. Virtually all of the mediators and are modulators of inflammation, able to amplify or attenuate the severity of inflammation. This is due to the complexity of their impact and their interaction with both the producer cells of these substances, and with each other. Accordingly, the mediator may be an additional effect (additive) potentiating (synergistic) and attenuating (antagonistic) interaction between neurotransmitters and their possible level of synthesis, secretion, or effects. Link is the main mediator in the pathogenesis of inflammation. It coordinates the interaction of many cells - effectors of inflammation, cell phase shift in the focus of inflammation. Accordingly, the pathogenesis of inflammation can be represented as a chain of multiple cell-cell interactions, regulated by mediators - modulators of inflammation.

All known mediators of inflammation in origin can be divided into humoral (formed in liquid medium - the blood plasma and tissue fluid) and cellular. The first group includes derivatives of complement, kinin, and clotting factors, to the second - vasoactive amines, derivatives of arachidonic acid (eicosanoids), lysosomal factors, cytokines (monokines), lymphokines, reactive oxygen metabolites, neuropeptides. .. While all the humoral mediators are pre existing, ie available as precursors to the last activation, including cell mediators can be identified as the pre-existing (deposited in the cells in an inactive state) - vasoactive amines lysosomal factors, neuropeptides, and again formed (ie, produced by cells when stimulated..) - eicosanoids, cytokines, lymphokines, active metabolites of oxygen.

Because humoral mediators of inflammation complement derivatives are the most important. Among the nearly 20 different proteins produced during complement activation directly related to inflammation are fragments C5a, C3a, C6 and C5-C9 complex. Thus C5a and C3a less are mediators of acute inflammation. C3 opsonizing pathogenic agent and thus promotes immune adhesion and

phagocytosis. Complex C5-C9 responsible for the lysis of microorganisms and abnormal cells. The source of complement are blood plasma and tissue fluid least. Increased supply of plasma complement the fabric is one of the most important appointments of exudation. Formed of C5a in the plasma and interstitial fluid under the influence of a carboxypeptidase N C5a des Arg C3a and increase the permeability of post-capillary venules. This C5a and C3a, being anaphylatoxin (t. E. Liberatore histamine from mast cells), increase the permeability of both directly and indirectly through histamine. Effect of C5a des Arg are not associated with histamine but is neutrodependent ie It carried by permeability factors released from polymorphonuclear granulocytes, - lysosomal enzymes, cationic and non-enzymatic proteins, reactive oxygen metabolites. Furthermore, C5a and C5a des Arg attract neutrophils. In contrast, virtually no C3a has chemotactic properties. Active complement components not only release of histamine, but interleukin-1, prostaglandins,

eukotrienes, platelet activating factor, and interact synergistically with prostaglandins and substance P.

Kinins - vasoactive peptides formed from kininogenov (α2-globulin) under the influence of plasma kallikrein (nona-peptide bradykinin) in the tissue fluid (lisilbradikinin decapeptide or kallidin). The trigger factor activation kallikreinkininovoy system is activated when tissue damage Hageman factor (XII coagulation factor), prekallikrein in converting kallikreins. Kinins mediate the expansion of arterioles and venules by increased permeability of endothelial cells contraction. They cut the smooth muscles of the veins and increase intracapillary and venous pressure. Kinins inhibit emigration of neutrophils, macrophages distribution modulate, stimulate mitogenesis and migration of T lymphocytes and the secretion of lymphokines. They also enhance proliferation of fibroblasts and collagen synthesis, and consequently, may be important in the pathogenesis of repair phenomena of chronic inflammation. One of the most significant effects of kinins - activation of reflexes by stimulating sensory nerve endings, which gives rise to inflammatory pain. Kinins cause or enhance histamine release from mast cells, prostaglandin synthesis in many types of cells, so some of their main effect - vasodilation, smooth muscle contraction, pain - is associated with release of other mediators, in particular prostaglandins.

Activation of Hageman factor triggers not only the process kininoformation but coagulation and fibrinolysis. Thus formed mediators such as fibrinopeptides and fibrin degradation products, which are potent hemattractant. Additionally, fibrinolysis and clot formation in blood vessels focus are significant as in the pathological and protective inflammatory phenomena.

Of primary interest cellular mediators cause eicosanoids, because most likely they are the central element of the mediator of the inflammatory response. This is supported by maintaining continuous production of eicosanoids in the outbreak, their close relationship with the key event of inflammation - leukocyte infiltration, a powerful anti-inflammatory effect their synthesis inhibitors. The main role in the production of eicosanoids in inflammation plays leukocytes, particularly monocytes and macrophages, although they are produced almost all types of nucleated cells upon stimulation of the latter. The predominant eicosanoids in inflammation is almost always turn out to prostaglandin (PG) E2, leukotriene (LT) B4 and 5-hydroxyeicosatetraenoic acid (5-HETE). Also formed, albeit in smaller quantities, thromboxane (TX) A2 ShT2a, PGB2, prostacyclin (PG12), LTC4, LTB4, LTE4, other HETE.

The main effects of eicosanoids in inflammation are the effects on white blood cells. PG and LT particularly as potent hemattraktanty thus play an important role in the mechanisms of self-maintenance of leukocyte infiltration. PG do not increase the vascular permeability, but being strong vasodilators, increase flushing and hence exudation. LTC4, LTB4, LTE4 increase the permeability of blood vessels by direct contraction of endothelial cells and the LTB4 - both neutrophil-dependent mediator. PG and LT are important in the genesis of inflammatory pain. This PGE2, without having

direct painful activity, increases the sensitivity of receptors of the afferent pain nerve endings to bradykinin, and histamine. PGE2 is a potent fever agent in inflammation and fever may be partly due to its release. PG play a key role in the modulation of the inflammatory process, realizing bi-directional regulation of exudation, emigration and degranulation of leukocytes, phagocytosis. For example, PGE can potentiate the development of edema induced by histamine or bradykinin, a nrF2a, by contrast, weaken. Similar relationships between PGE and nrF2oc also apply to the emigration of leukocytes.

Particularly wide range of interactions with other mediators of inflammation is characteristic for LT. They interact synergistically against bronchoconstriction with histamine, acetylcholine, PG and TCS, stimulate the release of PGs and TCS. Eicosanoids modulator function via the change in the ratio of cyclic nucleotides in the cells.

The sources of histamine are basophils and mast cells. Serotonin (neurotransmitter) in humans, except for minor quantities in mast cells, also found in the enterochromaffin cells and platelets. Due to the rapid release during the degranulation of mast cells, the ability to change the lumen of microvessels and cause immediate contraction of endothelial cells of venules histamine and serotonin are considered to be key mediators initial microcirculatory disturbances in the focus

of acute inflammation phase and immediate increase of vascular permeability. Dualistic histamine plays a role as regards vessels and cells. Through H2 receptor it dilates arteriolar and by H1-receptors narrows venules and thus increases vnutrikapillyarnoe pressure. A histamine H1-receptor stimulates, and a H2-receptor inhibits degranulation and emigration of leukocytes. In the usual course of inflammation Histamine acts predominantly via H2 receptors on neutrophils, limiting their functional activity, and through the H1-receptor on monocytes, stimulating them. Thus, along with vascular pro-inflammatory effects, it has anti-inflammatory effect. Serotonin stimulates monocytes in inflammation. Histamine performs bidirectional regulation of proliferation, differentiation and functional activity of fibroblasts and hence may be of importance in the reparative phenomena. Modulatory effects and histamine mediated by cyclic nucleotides.

With regard to the interaction of biogenic amines in the inflammation, it is known that histamine via the H1-receptor can trigger or enhance the synthesis of prostaglandins, and through H2 receptors - to oppress. Interacting among themselves and with bradykinin, nucleotides and nucleosides, substance P, biogenic amines increase vascular permeability. vasodilator action of histamine is enhanced in combination with acetylcholine, serotonin, bradykinin.

The main source of lysosomal enzymes in inflammation are phagocytes - granulocytes and monocytes-macrophages. Despite the great importance of phagocytosis in the pathogenesis of inflammatory phagocytes are, first of all, the carrier mobility of mediators - modulators secreted extracellularly. The release of lysosomal contents carried in their stimulation of chemotaxis, migration, phagocytosis, damage, death. The main components of human lysosomal proteases are neutral - elastase, cathepsin G and collagenase contained in primary azurophilic, granules of neutrophils. In the process of antimicrobial protection, including during inflammation, proteases belong to the "second stage" oxygen-factor after (myeloperoxidase - hydrogen peroxide) and oxygen independent mechanisms such as lactoferrin and lysozyme. They provide mainly lysis already killed microorganisms. The main effects of the protease - mediation and modulation of inflammation, including damage to its own tissues. Mediator and modulatory effects of proteases are made in relation to vascular permeability, emigration, phagocytosis.

Increased vascular permeability under the influence of lysosomal enzymes is due to lysis subendothelial matrix thinning and fragmentation of endothelial cells and is accompanied by hemorrhage and thrombosis. By forming or cleaving essential chemotactic substances, lysosomal enzymes are modulators of leukocyte infiltration. Lysosomal enzymes, depending on the concentration, may themselves enhance or inhibit the migration of neutrophils. With respect to

phagocytosis neutral proteases also have a number of effects. In particular, the elastase may form opsonin C3, which is also important for the adhesion of the particles to the surface of the neutrophil. Consequently, the neutrophil itself currently provides a mechanism to increase phagocytosis. How cathepsin G, elastase and increase the affinity of Fc-receptor complexes to neutrophil membranes immunoglobulins and thus enhance the efficiency of absorption of the articles.

With the ability to activate lysosomal enzymes of the complement system, kallikrein-kinin, and coagulation fibrinolysis, release cytokines and lymphokines and inflammation develops self-sustaining for a long time.

The most important property of cationic nonenzymatic proteins contained in both azurophil and specific granules in neutrophils, is their high microbicidal. In this respect, they are in a synergistic interaction with myeloperoxidase system - hydrogen peroxide. Cationic proteins adsorbed on the negatively charged bacterial cell membrane by electrostatic interactions. As a result, violated permeability and membrane structure and the death occurs of a microorganism that is a prerequisite for further efficient lysis it lysosomal proteases. The released cationic proteins mediate increased vascular permeability (mainly by inducing mast cell degranulation and histamine release), the adhesion and emigration of leukocytes.

The main source of cytokines (monokines) in inflammation are stimulated monocytes and macrophages. Further, these polypeptides are produced by neutrophils, lymphocytes, endothelial and other cells. The most studied cytokine is interleukin-1 (IL-1) and tumor necrosis factor (TNF). Cytokines increase vascular permeability (neutrodependent path), the adhesion and emigration of

leukocytes. In addition to the pro-inflammatory properties of cytokines may play a role in the direct protection of the body, stimulating the neutrophils and monocytes to the killing, the absorption and digestion of microorganisms intruded, as well as enhancing phagocytosis by opsonization of the pathogenic agent. Stimulating wound cleansing, proliferation and differentiation of cells, cytokines enhance the reparative processes. In addition, they may mediate tissue destruction (degradation of cartilage matrix and bone resorption) and, therefore, play a role in the pathogenesis of connective tissue diseases, particularly rheumatoid arthritis. Action cytokines cause a number of metabolic effects underlying the common manifestations of inflammation -.. Fever, sleepiness, anorexia, changes in metabolism, stimulation of hepatocytes to increased synthesis of acute phase proteins, activation of the blood system, etc. Cytokines interact with prostaglandins, neuropeptides and other neurotransmitters.

For inflammatory mediators (cytokines) provides a number of lymphokines - polypeptides produced by stimulated lymphocytes. The most studied of lymphokines that modulate the inflammatory response is a factor depressing macrophages macrophage activation factor, interleukin-2. Lymphokines coordinate the interaction of neutrophils, macrophages and lymphocytes, regulating thereby the inflammatory response in general.

Reactive oxygen metabolites, primarily free radicals - 0- superoxide anion radical, hydroxyl radical N0-, perhydroxil N02-, due to the presence on their outer orbit of one or more unpaired electrons have high reactivity with other molecules and therefore considerable destructive potential which It has a role in the pathogenesis of inflammation.

The source of free radicals and other oxygen-derived inflammatory mediators and modulator - hydrogen peroxide (H_20_2), singlet oxygen (0_2-), hypochlorite (N0S1) - are: respiratory burst of phagocytes in their stimulation, arachidonic acid cascade in the formation of eicosanoids , enzymatic processes and peroxisomal endoplasmic reticulum, mitochondria, cytosol, as well as auto-oxidation of small molecules, such as hydroquinones, leukoflavine, catecholamines, etc..

The role of active oxygen metabolites in inflammatory consists, on the one hand, increase in phagocyte bactericidal capacity, the other - into their mediator and modulatory functions. Mediator role of reactive oxygen metabolites due to their ability to cause lipid peroxidation, oxidation of

proteins, carbohydrates, nucleic acid damage. Such molecular changes underlying induced reactive oxygen metabolites phenomena characteristic of inflammation - increasing vascular permeability (due to damage to endothelial cells), the stimulation of the phagocytes. Modulatory role of active oxygen metabolites can be to strengthen both inflammation (release of enzyme induction by and interaction with them in the damaged tissue), and anti-inflammatory effects (due to inactivation of the lysosomal hydrolases and other inflammatory mediators). Of great importance are the active oxygen metabolites in the maintenance of chronic inflammation.

By inflammation mediators and modulators also include neuropeptides - substance released by C-fibers as a result of the activation of the inflammatory agent polymodal nociceptors, which play an important role in the occurrence of axon reflexes in the final branched primary afferent (sensory) neurons. The most studied are substance P, calcitonin-gen connected peptide neurokinin A. Neuropeptides increased vascular permeability, and that their ability to largely mediated by mediators derived from mast cells. Nonmyelinic between nerves and mast cells have membrane contacts that provide a message to the central nervous system inflammation. Neuropeptides interact synergistically to increase vascular permeability, both among themselves and with histamine, bradykinin, C5a, platelet-activating factor, leukotriene B4; antagonistically - ATP and adenosine. They also have a potentiating effect on attracting and cytotoxic function of neutrophils, increase the adhesion of neutrophils to the endothelium of venules. Furthermore, neuropeptides nociceptors increased sensitivity to various mediators, including prostaglandin E2 and prostacyclin participating thereby recreating in inflammatory pain.

In addition to these substances, to inflammatory mediators are also acetylcholine and catecholamines that are released when excited choline - and adrenergic structures. Acetylcholine causes dilation of blood vessels and plays a role in axon reflex mechanism of arterial hyperemia in

inflammation. Norepinephrine and epinephrine inhibit the growth of vascular permeability, acting mainly as a modulator of inflammation.

Disorders of blood circulation and microcirculation in the inflamed tissue

Microcirculation disorders. Vascular phenomena develop after exposure to the inflammatory agent since the initial ones are inherently reflex. They tracked well under the microscope in a classic experiment on the frog's mesentery Cohnheim and include a number of stages:

1. Short-term spasm of arterioles, accompanied by tissue blanching. It is the result of reflex excitation of the vasoconstrictor effects of the inflammatory agent. It lasts from a few tens of seconds to several minutes, so it is not always possible to note.

2. Arterial hyperemia, caused by the expansion of the arterioles, the mechanism of which, on the one hand, is associated with axon reflex stimulation of vasodilators, and on the other - with direct vasodilating effects of inflammatory mediators:. Neuropeptides, acetylcholine, histamine, bradykinin, prostaglandins, etc. Arterial hyperemia is the basis of two main external signs of local inflammation - redness and increase tissue temperature. Further, in the reconstruction of the heat value is increased in the hearth heat production due to increased metabolism.

Mechanisms of arterial hyperemia:

1. Neuroparalytic mechanism:

Lowering the sensitivity vasoconstrictive α - adrenergic receptors to norepinephrine vessels → «overweight» vasodilator receptors (β - adrenergic receptors, cholinergic receptors, etc.) → expansion of the arteries.

2. Neurotonic mechanism:

Stimulation of sensory receptors on pathological factors → the axon reflex → (release of mediators - neuropeptides (substance P, neuropeptide Y, neurokinin A) on the reflex efferent fibers → dilation of the arteries.

Irritation from PF efferent vasodilator nerves.

3. Neurohumoral mechanisms:

Progress within the axon - reflex → neuropeptides stimulate the formation of histamine on mast cells → stimulation of endothelial histamine H-receptor → synthesis and release NOº → dilation of the arteries.

4. The humoral mechanism:

Pathological factors, damaging and activating cells at the site of injury, resulting in the formation of histamine, prostaglandin E, E2, bradykinin, Nº, Kº → expansion arteries.

3. Venous congestion. It can develop within a few minutes after exposure to the inflammatory agent, however, is characterized by a considerable length - is accompanied by the entire course of the inflammatory process. At the same time, as if her participation is the main inflammation, it is considered a true inflammatory hyperemia.

Mechanism of venous congestions may be within the vascular and extravascular.

1) Intravascular:

- The swelling of the vascular wall.
- Swelling of blood cells.
- Near-wall distance of leukocytes.
- Activation of coagulation factor XII → thrombus formation.
- Thickening of blood from the vascular permeability ↑ (fluid outlet) → slowing blood flow → slowing down the outflow of blood.

2) Extravascular:

- Compression of veins outside exudate.
- The weakening of the connective tissue framework around veins → collaps veins (elastase, collagenase).
- Reducing venules influenced F2a, serotonin, histamine.

In the mechanism of venous congestion, there are three groups of factors:

a) violation of rheological properties of blood and its circulation itself. These include increasing the viscosity of the blood due to its thickening caused by exudation, loss of albumin, globulin increase in the content, change the state of colloidal proteins; strengthening the resistance to blood flow as a result of the regional state of leukocytes, swelling and aggregation of red blood cells; thrombus formation due to the activation of blood coagulation; violation of the nature of blood flow - a slowdown of blood flow in the axial zone, reducing the edge of the plasma zone;

b) changes in the vascular wall, which include loss of vascular tone due to paralysis of the neuromuscular apparatus of vessels; decrease in the elasticity of the vascular wall; endothelium swelling and increasing its adhesiveness, causing vascular lumen narrowing, the conditions for the adhesion of leukocytes to the endothelium;

c) Changes in tissue, consisting in compression of venules and lymphatic vessels edema, infiltrated tissue; reducing elastic connective tissue.

It should be noted that many of these factors are, on the one hand, the immediate causes, but on the other - both consequences of developing venous congestion.

Inflammatory hyperemia is different from other kinds of congestion (caused, for example, a mechanical factor) significant weakening or even a perversion of the reaction vessels of inflamed tissues to the action of vasoconstrictor agents (adrenaline, caffeine) and the stimulation of the sympathetic nerves. This phenomenon may be due to the "desensitization", or tachyphylaxis, vessels, i.e. reduced or qualitative change in their sensitivity to the action of vasoconstrictor stimuli caused by

the blockade of receptors. Other differences between the inflammatory hyperemia associated with a pronounced hyperemia of the inflamed organ or tissue site, the expansion and increase in the number of functioning capillaries, the intensity of microcirculation, delay linear blood flow velocity, etc., That can be considered inflammatory hyperemia as a special kind of microcirculation disorders.

4. Stasis. It can develop in certain ramifications of the vessels of inflamed tissue. A common characteristic of stasis acute, rapidly developing, for example hyperergic, inflammation. Usually, blood flow disturbance in inflammatory stasis is transitory, but in the event of damage to the vascular wall and blood clots in many microvessels stasis becomes irreversible.

Exudation and exudates

Disorders of microcirculation in inflammation accompanied by the phenomena of exudation and emigration.

Exudation (exsudatio from Latin exsudare - Sweat) - exudation of protein-containing liquid portion of the blood through the vascular wall into the inflamed tissue. Accordingly, the fluid exiting at an inflammation of blood vessels in tissue, called exudate. The terms "exudates" and "exudation" are used only to inflammation. They are designed to emphasize the difference between the inflammatory fluid (and the mechanism of its formation) of interstitial fluid and transudate - noninflammatory effusions leaving for other, non-inflammatory, edema. If transudate contains up to 2% of the protein, the exudate - more than 3 to 8%.

Mechanism exudation consists of three main factors:

1) increased vascular permeability (capillaries and venules) from exposure to mediators of inflammation and in some cases the most inflammatory agent;
2) an increase in blood (filtration) the pressure in the blood vessels due to inflammatory focus hyperemia;
3) an increase in osmotic and oncotic pressure in the inflamed tissue as a result of alteration and exudation started and may decrease blood oncotic pressure due to the loss of proteins with abundant exudation.

Exudation leading factor is the increase in vascular permeability. It usually occurs in two phases - an immediate and delayed. The first action occurs after the inflammatory agent reaches a maximum over several minutes and is completed in an average of 15-30 minutes, when the

permeability may return to normal (in the event that flogogen itself has no direct influence on damaging vessels). The second phase develops gradually, reaching a maximum after 4-6 hours and lasts sometimes up to 100 hours depending on the type and intensity of inflammation. Consequently, the exudative phase of inflammation is started immediately after exposure flogogena and lasts more than 4 days.

Transient increase in vascular permeability in the immediate phase mainly due to contractile phenomena by endothelial cells. In the reaction involved predominantly venules. As a result of the interaction of mediators with specific receptors on the membranes of endothelial cells is a reduction of actin and myosin microfilaments cytoplasm of cells and endothelial cells are rounded; two adjacent cells move away from each other, and between them there between endothelial slot through which is carried and exudation. Persistent increase in vascular permeability in the delayed phase is associated with damage to the vascular wall leukocyte factors - lysosomal enzymes and active oxygen metabolites. In this case the process involved not only venules, and capillaries.

With respect to vascular permeability, inflammation mediators may be divided into two groups: 1) direct-acting affecting directly on endothelial cells causing their contraction - histamine, serotonin, bradykinin, C5a, SCAs, leukotrienes C4 and D4; 2) neutrophil dependent whose effect is mediated leukocyte factors. These mediators are not able to increase vascular permeability in animals leukopenic. This complement component C5a des Arg, leukotriene B4, cytokines, notably interleukin-1, partly platelet activating factor.

Increased vascular permeability in combination with the increased blood pressure filtration and osmotic and oncotic pressure tissue provides an outlet from the liquid portion of the blood vessel and its retention in the fabric. According to some exudation it is also carried out by filtration and diffusion through micropores in themselves endothelial cells (transcellular channels), and not so much a passive way as active - through so-called microvesicular transport, consisting mikropinotsitoze endothelial cells of blood plasma and its transport as microbubbles (microvesicles) toward the basal membrane and release (extrusion) in its cloth (AM Chernukh).

Since the increase in vascular permeability is observed in inflammation to a greater extent than any of the non-inflammatory edema, even when that factor is leading, in the amount of protein in the exudate exceeds that transudate. In turn, the difference in the degree of increase in vascular permeability in inflammatory and non-inflammatory edema due to the difference in the amounts set and released biologically active substances. For example, leukocyte factors that damage the vascular wall play an important role in the pathogenesis of exudation and little involved with non-inflammatory edema.

The degree of increase in vascular permeability and is determined by the protein composition of exudate. With a relatively small increase in permeability can only leave fine albumin, as further increasing - globulins and finally fibrinogen.

Depending on the qualitative composition of the following types of exudates: serous, fibrinous, purulent, putrid, bloody, mixed.

Characterized serous exudate moderate protein content (3.5%), mainly particulate (albumin), and a small amount of polymorphonuclear leukocytes, thereby has a low specific gravity (1015-1020), and is sufficiently transparent. On the composition most similar to transudate. Characterized by inflammation of the serous membranes (serous peritonitis, pleurisy, pericarditis, arthritis and others.), It is less common in inflammation in parenchymal organs. Serous exudate with inflammation of the mucous membranes is characterized by a large admixture of mucus. This inflammation is called catarrhal (from the Greek katarrheo - flock, flow down. Catarrhal rhinitis, gastritis, enterocolitis, etc.). Most often serous exudate observed during the burn, viral, allergic inflammation.

Fibrinous exudate is rich in fibrinogen, which is the result of a significant increase in vascular permeability. Upon contact with the damaged tissue fibrinogen is converted to fibrin and falls as villous mass (by serous membranes) or film (mucous), whereby the exudate is compacted. If fibrinous film is loosely, surfactants, can be easily separated without disturbing the integrity of the mucous membrane, such inflammation is called lobar. It is observed in the stomach, intestines,
trachea, bronchi. In the case where the film is tightly soldered to the underlying tissue and its removal exposes the ulcer surface, it is a diphtheritic inflammation. It is characteristic of the tonsils, mouth, esophagus. This difference is due to the nature of the mucosal epithelium and the depth of damage. Fibrinous films may be rejected due to spontaneous autolysis deployed around the hearth, and the demarcation inflammation and to go outside; subjected to enzymatic melting or organization, ie. e. the germination of the connective tissue with the formation of connective tissue adhesions or adhesions. Fibrinous exudate may be observed in diphtheria, dysentery, tuberculosis.

Purulent exudate is characterized by a large number of polymorphonuclear leukocytes, mostly dead and destroyed (pus cells), enzymes, autolysis tissue products, albumin, globulin, sometimes strands of fibrin, especially nucleic acids, causing the high viscosity of pus. Consequently, purulent exudate is quite cloudy, with a greenish tinge. It is characteristic of the inflammatory processes caused coccal infection by pathogenic fungi or chemical phlogogen, such as turpentine, toxic substances.

Putrid exudate characterized by the presence of food putrefaction of tissues, resulting in a dirty-green color and a bad smell. Formed in the event of the accession of pathogenic anaerobes.

Hemorrhagic exudate is characterized by a high content of red blood cells, which gives it a pink or red color. Characteristic tuberculous lesions (tuberculous pleurisy), plague, anthrax, smallpox, influenza toxic, allergic inflammation, t. E. For the impact of highly virulent agents, rapidly flowing

inflammation, accompanied by a significant increase in the permeability of blood vessels and even destruction. Hemorrhagic character can take any kind of inflammation - serous, fibrinous, purulent.

Mixed exudates observed in inflammation occurring on the background of weakening the body's defenses and thereby joining a secondary infection. There are seroplastic, seropurulent, serous-hemorrhagic, purulent fibrinous exudates.

The biological significance of exudation is that, being one of the main components of inflammation as a pathological process, it carries with it an important protective role, which is as follows. Exudation ensures delivery into the tissue plasma mediators - the active components of the complement, kinin, coagulation factors, plasma enzymes, biologically active substances released by activated blood cells. Together with the tissue mediators are involved in the killing and lysis of microorganisms, attracting white blood cells, opsonization of pathogenic agent, stimulation of phagocytosis, wound cleansing, reparative phenomena. With the exudate from the blood stream into the center out metabolic products, toxins, t. E. The focus of inflammation, performs a drain eliminative function. On the other hand, due to the coagulation of lymph in the hearth, fibrin deposition, and worsening of venous stasis venous thrombosis and lymphatics exudate in the delay involved in the outbreak of microbes, toxins, metabolic products.

However, under certain conditions, can lead to exudation of inflammatory complications - entry of fluid in the body cavity with the development of, for example, pleuritis, pericarditis, peritonitis; compression of nearby organs; pusformation with the development of an abscess, empyema, cellulitis. Education adhesions can cause displacement and disruption of organ function. Of great importance is the localization of the inflammatory process. For example, education on the mucous membrane of the larynx in diphtheria fibrinous exudate can lead to asphyxiation.

The accumulation of fluid in the tissues causes a local external sign of inflammation is swelling. In addition, along with the action of bradykinin, histamine, prostaglandins, neuropeptides exudate on pressure-sensitive nerve endings has a value in the occurrence of inflammatory pain.

Out of leukocytes into the inflamed tissue (emigration of leukocytes)

Emigration (emigratio from Latin emigrare - To move out, move) - white blood cells out of the blood vessels in the tissue. It implemented by diapedesis mainly through the wall of venules. The emigration of leukocytes into the hearth is a key event in the pathogenesis of inflammation. White blood cells are the major effectors of inflammation. Extracellular bactericidal and lytic effects of leukocyte phagocytosis of products and play a crucial role in the fight against phlogogen. At the same time, affecting the cells and blood vessels, leukocyte components act as important
modulators and mediators of inflammation, including damage to its own tissues. By wound cleansing, phagocytes and their products create preconditions for reparative phenomena, which also play a role in stimulating proliferation, differentiation and functional activity of fibroblasts and other cells. emigration mechanism is chemotaxis phenomenon (I.I. Mechnikov).

Stage emigration of leukocytes:

Stage 1 (parietal state of leukocytes)

Stage 2 (the passage of leukocytes through the vessel wall)

Stage 3 (movement of leukocytes outside the vascular wall to the center of the source of inflammation)

Stage 4 (phagocytosis)

Starting torque activation of phagocytes is the impact on receptors (often specific) cell membranes of various chemotactic agents released by microorganisms or phagocytes, as well as resulting in the tissue as a result of an inflammatory agent or under the influence of phagocytes themselves.

The most important fragments are hemattraktant complement fibrinopeptides and degradation products of fibrin, kallikrein, plasminogen proactivator, fragments of collagen, fibronectin, arachidonic acid metabolites, cytokines, lymphokines, bacterial peptides, granulocyte decay products.

As a result, hemattraktant binding to receptors and activation of enzymes in the plasma membrane of phagocyte develops breathing (respiratory, metabolic) explosion, consisting in a sharp increase in oxygen consumption and the formation of active metabolites. This process is not related to providing phagocyte energy. It aims to adopt additional phagocyte highly reactive toxic substances more effectively kill microorganisms. Along with the respiratory burst of other changes occur in the phagocyte. These include increased production of specific membrane glycoproteins that define the adhesiveness phagocyte, lowering the surface tension of the membrane and the change of the colloidal state of the cytoplasm areas (reversible transition from a gel to a sol), which creates conditions for the formation of pseudopodia; activation of actin and myosin microfilaments underlying migration; enhanced secretion of substances from the separation facilitating attachment of leukocytes to the endothelium, such as lactoferrin, cationic proteins, fibronectin, interleukins.

White blood cells out of the blood of the axial current in the plasma. This contributes to the violation of the rheological properties of blood, slowing blood flow, the change in his character, in particular the reduction of the edge of the plasma zone.

As a result of increasing the adhesive properties of leukocytes not only, but primarily and mainly endothelial cells occur leukocyte adhesion to the endothelium evolving phenomenon of the regional state of leukocytes.

Increased endothelial adhesiveness may be due to their enhanced production of adhesion glycoproteins (lectins) and other substances which are included in a fibrin film normal by the endothelium overlying the lumen. It is also envisaged that it may be associated with detent on endothelial cells hemattraktant subsequently interacting with specific receptors on leukocytes, or with increased expression on endothelial receptor for immunoglobulin G and complement fragments C3, resulting in fixation here first IgG and C3, and already to them - leukocytes which also have receptors for IgG and C3.

Initial contact of leukocytes with the endothelium is very fragile, so that under the influence of the blood flow, they can be rolled over the surface of the fibrin film, but the contact is consolidated quickly. Some importance is attached to the electrostatic forces. As a result of the activation of the negative charge of leukocyte reduced, which reduces the force of mutual repulsion between them and endothelial cells, are also having a negative charge. This, in turn, creates the conditions for the formation between leukocytes and endothelium calcium bridges.

According to some reports, Ca2 + and other divalent ions may play a key role in the adhesion of leukocytes.

The winners of the boundary position of the white blood cells produce pseudopodia that penetrate the between endothelial gap, and thus "shimmer" through the endothelial layer. Increased vascular permeability and fluid flow from the vessel into the tissue play a role contributing factors emigration: the stronger the passage easier for leukocyte vascular wall. However, emigration - the process is fully active. It requires power and is carried out with increased oxygen consumption and involving calcium and magnesium ions, necessary for the contractile effects in the leukocyte. Once between the endothelial layer and the basement membrane, leukocyte lysosomal proteinase allocates dissolving it, and cationic proteins, altering colloidal state basement membrane (reversible transition from gel to sol), that provides increased permeability of its leukocyte. Immigrated white blood cells are separated from the outer surface of the vascular wall and amoeboid movement directed towards the center of the source of inflammation, which is determined by the concentration gradient of chemotactic substances in the hearth. Some may play a role electrokinetic phenomena caused by the potential difference between the negatively charged white blood cells and the positive charge of the fabric characterized - hyperoncia H +.

Initially among exudation of leukocytes in acute inflammation predominate focus granulocytes, mostly neutrophils, and then - monocytes-macrophages. Later in the outbreak are accumulated lymphocytes.

Since the slowing of blood flow in certain ramifications of the microvasculature and the boundary distance leukocytes can develop very quickly, and migrating neutrophil enough 3-12 minutes to pass the endothelium, the emergence of granulocytes in the outbreak could occur as early as the 10th minute of the onset of inflammation. The rate of accumulation of neutrophils in the focus is the highest in the first two hours, gradually decreasing in the following. Their number reaches a maximum after 4-6 h. During this period, the neutrophil leucocytes hearth represented more than 90%. Granulocytes phagocytose bacteria or other foreign bodies and particles of dead cellular elements carrying across supply extracellular enzymes, cationic proteins, reactive oxygen metabolites. Simultaneously, the massive destruction of neutrophils, which remains an important incentive to appear expansion infiltration as neutrophil and monocyte. As is normal, the majority of granulocyte, published in the fabric is never returned to the bloodstream.

Monocytes usually predominate in the outbreak of acute inflammation after 16-24 hours and reach a peak, usually at 3-rd day. However, migration of monocytes from the blood into the tissue starts simultaneously with neutrophil migration. It is assumed that initially smaller than the neutrophils, monocyte accumulation rate associated with the inhibition of monocyte chemotactic neutrophil influenced waste products within a certain time required for full expression of neutrophil responses and prevent its monocytic control. In the middle of inflammation observed the gradual transformation immigrated monocytes into macrophages and maturation of the latter, in the course of which the volume of the cytoplasm and organelles in it is increased; in particular, it increased the number of mitochondria and lysosomes, which are essential for the proper performance of their functions of macrophages in the hearth. Growing pinocytosis activity in the cytoplasm of an increasing number of phagolysosomes, increases the number of filopodium. Monocytes, macrophages are also a source of inflammatory mediators (enzymes, oxygen metabolites, cytokines) phagocytose bacteria, but have precedence remains in phagocytosis of dead cells, in particular neutrophils. Therefore clear dependence of accumulation of monocytes from the previous release of neutrophils. Thus, in neutropenic rabbits do not appear monocytes in inflammation for 16 h, while in vivo inflammation detected by the 4th hour, and the introduction in the animal leykopenicheskim neutrophil inflammatory focus restores normal accumulation of mononuclear cells. Also known chemotactic effects on neutrophils monocytes lysate, partly due to the cationic protein lysosomal granules.

On the other hand, neutrophil accumulation is largely dependent on monocytes. Especially, apparently, it concerns the portion of neutrophil infiltration, which is associated with increased hematopoiesis, since the latter initiates monocyte-macrophage hematopoietic factors, such as interleukin-1, and various types of so-called growth factors - substances mainly of a protein nature, are responsible for the proliferation and differentiation in bone marrow hematopoietic cells.

Currently, a number of chemotactic peptides isolated from human monocytes neutrophils, which may belong to a role in the mechanism of self-regulation of leukocyte inflammatory reaction chamber. However, the question of the mechanisms of cell change in the inflammation phase, the transition from the deployment of the inflammatory response to its resolution refers to the least studied in the inflammation problem.

Cellular composition of exudate to a large extent depend on the nature and course of the inflammatory process, in turn, determined by the inflammatory agent and the state of reactivity. Thus, the exudate is particularly rich in neutrophils, if the inflammation is caused by pyogenic microbes; in allergic inflammation in the hearth contains many eosinophils. Chronic inflammatory processes are characterized by low content of neutrophils, monocytes and lymphocytes predominance.

Immigrating leukocytes in conjunction with the local origin proliferating cells form inflammatory infiltrate. This exudate with cells contained therein infiltrates the tissue, are distributed among the elements of the inflammatory site and making it tight and dense. Infiltrate along with exudate causes swelling and has a value in the occurrence of inflammatory pain.

Phagocytosis was discovered and understood as an essential element of inflammation and innate immunity II Mechnikov in 1882.

II Mechnikov identified 4 phases of phagocytosis:

1) approach phase exit of leukocytes from the vessel and the approach to the object under the influence of phagocytosis hemattraktant;
2) attachment phase (contact);
3) immersion phase enveloping and immersing the object into the phagocyte; formed a special vacuole, where lysosomes accumulate;
4) phase of digestion, the result of which can be 2 variants of outcomes: a) adequately dosed release of lysosomal enzymes, destroying only flogogen (phagocyte itself remains intact); b) excessive secretion of lysosomal enzymes that leads to the destruction of the object and the macrophage phagocytosis.

Phagocytes interacting with bacteria, are activated, their membrane becoming "sticky" because the number of different receptors on it dramatically increases and increases as the 'probed' mobility cytoplasm of these cells. Simultaneously accumulate in the cytoplasm and peroxisomes granules filled with potent proteases. When such a cell is encountered with microorganisms, bacteria "sticks" to the surface of the phagocyte, enveloped by its pseudopodia and is inside the cell, where it is destroyed. Macrophages start to allocate Wednesday tumor necrosis factor (TNF), interferon-γ (IFN-γ) and IL-8, which plays in inflammation special role - it gives rise to endothelial receptors that react with monocytes and neutrophils with high affinity so that these cells capillary stop within the area of inflammation. IL-8 is most effective for creating a gradient chemotaxis of phagocytic cells. Phagocytes have receptors for IL-8, which are "feel" the difference in concentration on the side facing towards its source, and on the opposite side, and guide its movement along the axis of the maximum difference. Thus phagocytic cells accumulate in the inflammation, actively absorb and destroy (intracellular), bacteria and fragments of cells and secrete enzymes that destroy the intercellular substance of connective tissue. When festering skin surrounding the focus of inflammation (abscess), thins and breaks: flogogeny, cell debris and accumulated phagocytes are released from the body. Struck by the tissue site is gradually being restored. By removing the remains of the destroyed white blood cells and tissue macrophages eliminate a major source of private chemotactic stimulation and suppress the further development of the local leukocyte reaction. As purification inflammatory focus of macrophages decreases the amount of the reduction of their blood supply. From the hearth, they are carried away by the current of lymph recovering in regional lymph nodes, where the die. Lymphocytes part die part converted into plasma cells producing antibodies, and then gradually eliminated.

Restorative processes in inflamed tissue

Proliferation (proliferatio from Latin proles - progeny, ferre - To create). Under inflammatory proliferation understand multiplication of cellular elements in the local inflammation. Proliferation develops from the outset along with inflammation phenomena of alteration and exudation, but it becomes dominant in the later period of the process, at least subsided exudative-infiltrative phenomena. Initially, it is largely expressed in the periphery of the hearth. The most important condition is a progressive proliferation of purification efficiency inflammatory focus on microorganisms or other harmful agents, alterations in tissue products, dead white blood cells (wound cleansing). The leading role in this is given macrophages - hematogenous (monocytes) and tissue (histiocytes) origin.

Wound cleansing takes place mainly through the extracellular degradation of damaged tissue, as well as by phagocytosis. It is carried out burrows, regulatory influence of cytokines using enzymes such as proteoglycanase, collagenase, gelatinase. Activation of these enzymes may occur under the influence of the plasminogen activator, with the participation of cytokines released from mesenchymal cells. Prostaglandins, releasing together with enzymes, may, for its part, to induce proteinase and to contribute to the degradation processes. Eliminating the remains of the destroyed white blood cells and tissue macrophages eliminate one of the major sources of their own chemotactic stimulation and suppress the further development of the local leukocyte reaction. As purification inflammatory focus of macrophages amount decreases due to lower revenues from their blood. From the hearth, they are carried away by the current of lymph recovering in regional lymph nodes, where the die. Lymphocytes part die part converted into plasma cells producing antibodies, and then gradually eliminated.

Proliferation is mainly due to the mesenchymal stromal cells and cells of the parenchyma organs. It involves cambial, adventitial endothelial cells. As a result, differentiation of stem cells of the connective tissue - polyblasts - appear in the hearth epithelioid cells, fibroblasts and fibrocytes. The main cellular elements responsible for repair processes in inflammation, are fibroblasts. They produce extracellular basic substance - glycosaminoglycans, as well as synthesize and secrete a fibrous structure - collagen, elastin, reticulin. In turn, collagen is the main component of scar tissue.

Proliferation processes are under the control of humoral complex. Crucial here are again macrophages. They are a major source of fibroblast growth factor - termolabilnogo protein that stimulates fibroblast proliferation and collagen synthesis. Macrophages also enhance the attraction of fibroblasts into the inflammatory focus. An important role played by fibronectin secreted by macrophages, and IL-1. Macrophages stimulated proliferation of endothelial and smooth muscle cells, and basement membrane, thus forming microvessels. Inhibition or stimulation system of mononuclear phagocytes, respectively decreases or increases the development of granulation tissue in the focus of purulent inflammation.

In turn, macrophages mediate regulatory effect on proliferation of fibroblasts and T-lymphocytes. The latter are activated by proteases, formed in the inflammation as a result of tissue breakdown. Proteinases may directly affect both macrophages and fibroblasts. Macrophages and lymphocytes can release mono - and lymphokines, not only stimulating but also depressing fibroblasts, acting as a true regulator of their functions.

Fibroblasts also depend on the platelet derived growth factor, which is a thermostable protein with a high content of cysteine and m. M. 30000 D. As other fibroblast growth factors called somatotropin, somatomedins, insulin-like peptides, insulin, glucagon.

An important role in proliferative phenomena play chalones - thermolabile glycoproteins with MM 40000 D, which are inhibitors of cell division. The mechanism of action is inactivation of enzymes involved in DNA replication. One of the main sources of chalones are segmented neutrophils. By decreasing the number of neutrophils in inflammation chalones content decreases, which leads to faster cell division. According to other assumptions, segmented neutrophils in inflammation almost chalones develop and produce hard antichalone (stimulants division); respectively, accelerates cell division, proliferation increases.

Other cells and mediators can modulate the reparative process, affecting the function of fibroblasts, macrophages and lymphocytes. Essential in the regulation of reparative phenomena also have reciprocal relations in the system of collagen - collagenase, stromal-parenchymal interactions (D.N. Mayansky).

Proliferation is replaced by regeneration. The latter is not in itself a complex inflammatory phenomena, but they should certainly difficult and inseparable from them. It consists in the growth of connective tissue, vascularization, to a lesser extent in the reproduction-specific tissue elements. With little tissue damage occurs relatively complete its regeneration. In the formation of the defect he is filled with granulation tissue at the beginning - the young, the rich blood vessels, which was later replaced with connective tissue scarring.

Chronic inflammation

Types:

1. Secondary (prolonged acute).
2. Primary chronic inflammation.

Secondary chronic inflammation.

Mechanisms of "pulling":

1. Untrained acute protective inflammatory response.
2. Improper treatment (antibiotic-resistant forms of microorganisms, long-term anti-inflammatory therapy).
3. Defects effectors of acute inflammation - neutrophils (syndrome Chediak - Higashi, Pelgera anomaly "lazy phagocytes syndrome", inherited granulomatous disease, lack of myeloperoxidase, glucose- 6FDG).
4. Violation exit monocytes (stress, burns).

Primary chronic inflammation

Etiology:

1. The reasons could be all those factors, which are not subject to full completion of phagocytosis:
2. Infectious agents (tuberculosis, leprosy, syphilis, toxoplasmosis, other protozoa, helminths, and their cysts).
3. Nonmetabolizing corpuscular material: foreign bodies, dust particles (silica, coal, talc).
4. The drugs hapten, antigenic nature - (HDT)

- the nature of the causative agent is not subjected to complete phagocytosis,
- dust-like structure of foreign bodies,
- place the causes of action (interstitial connective tissue)
- Local disorders of blood - and lymph circulation (ischemia, varicose veins, angiopathy in diabetes and others.)

There are cases where the inflammatory infiltrates in the outset is not accumulated polymorphonuclear leukocytes and monocytes, lymphocytes and their derivatives. The formation of such clusters of mononuclear cells, called "granuloma" is a prerequisite to a long course of inflammation. Chronic inflammation is an illustration of justice II remarks Mechnikov: "inflammation - a protective reaction in biological fact, but, unfortunately, do not always achieve perfection for the body."

In contrast to acute inflammation chronic inflammation begins not with microcirculatory disorders before the events described in the bloodstream, and from the accumulation of a critical mass of irritated (activated) macrophages in one place.

Persistent stimulation of macrophages can cause a variety of ways.

1. A number of microbes is absorbed by the macrophages, but once in their phagosomes, does not die and is able to persist for a long time and reproduce inside the cell (that pathogens of tuberculosis, leprosy, listeriosis, toxoplasmosis, and many others). Macrophages containing microbes, become the active state and begin to secrete inflammatory mediators.

2. Macrophages can absorb non-infectious particles that the cell is not able to break down or to throw on Wednesday (complex polysaccharide complexes - korragenan seaweed, dextran, zymosan from baker's yeast). Following intravenous administration to mice pellets zymosan they are captured by macrophages resident (Kupffer cells) of the liver and lung interstitial macrophages and activate them. After 2-3 days around these macrophages as epicenters around, begin to accumulate trapped blood monocytes and formed what is commonly called a granuloma, or mononuclear infiltrate. Attracting new monocytes / macrophages in activated macrophages localization zone associated with substances that cause chemotaxis. They are identified as active macrophages in finished form (LTC4, LTD4, PGE2) or a precursor C2, C4, C5, C6 complement components, which are converted to the C3a, C5a C567 fraction with high chemotactic activity by proteases secreted by the same macrophages.

Lysosomal enzymes are secreted by macrophages as collagenase cleaved collagen. The products of partial collagen degradation have a strong ability to attract fresh monocytes in the inflammatory focus.

Activated macrophages secrete bio-oxidant that initiate lipid peroxidation in the membrane of other cells in the infiltrated area. However, simply increasing chemotaxin in some tissue site has not meant to influx of new inflammatory effector cells from the blood. It is necessary that along with the formation of these substances occurred gradient increasing microvascular permeability, of which the mononuclear leukocytes could enter the area of irritated macrophages localize. Activated macrophages increased microvascular permeability, producing LTC4, LTD4, platelet aggregation factor, O2 -, collagenase and plasminogen activator, disintegrating capillary connective tissue barrier. They either decompact the capillary basement membrane, endothelial cells or reduce and expose the slit between endothelial or are one and the other way. This facilitates exit of leukocytes from the blood and their movement to chemotaxin high concentrations where they are attached to other cells infiltrate. Monocytes, coming to infiltrate secrete fibronectin. Thus, they are firmly bonded to the matrix of connective tissue, primarily collagen fibers. They seem to "get on the anchor." even has been called "anchoring" in English literature is the immobilization of cells (from English anchor -. anchor). This is a very important point, for "on the go" phagocytes "do not have time to solve the problems" that arise before them in the inflammation.

Phagocytosis occurs most effectively only when monocytes are fixed and spread on the connective tissue structures. Thus, not only the active trigger macrophages, but also dictate the process of chronic inflammation. However, in actual work in isolation macrophages, and in combination with other types of cells that are part of the inflammatory infiltrate (granuloma).

It is best studied in the functional cooperation between macrophages and lymphocytes:

1. First of all, these cells come into close cooperation in specific immune response develops when an infectious inflammation. Macrophages take up and partially destroy microbial antigens in their phagolysosomes. In a modified form of the antigen re-emerge on the macrophage plasma membrane, where they enter into a comprehensive communication with specific proteins. Only in such a combination the antigen recognized by T-lymphocytes. The interaction of macrophage and T-lymphocytes in chronic inflammation locus of antigen can be called. It manifests itself most visibly at those forms of chronic inflammation, which occur when the microbial infection and proceed with the phenomena of delayed-type hypersensitivity (DTH).

2. In addition, macrophages are associated with lymphocyte antigens not only in, but also through its secrets. Macrophages release substances (e.g., IL-1), lymphocyte growth enhancing and increasing their activity.

3. At the same time actively proliferating lymphocytes secrete lymphokines that activate macrophages and dramatically increase their effector function in the hearth of chronic inflammation:

- Inhibition of macrophage migration factor increases the adhesiveness of the membranes of macrophages and enables them to firmly cling to the substrate. The same factor Releasing the secretion of inflammatory mediators by macrophages;

- A factor that increases the aggregation of macrophages, their proliferation, the fusion of macrophages with each other to form a giant polynuclear cells, so characteristic of the foci of chronic inflammation. In particular, these cells are especially numerous in tuberculous infiltrates in the lungs;

- Lymphokines increase microbicide capacity of macrophages, and cells begin to kill the germs that before they parasitized with impunity. This is due to the fact that, firstly, lymphokines amplify the merger of phagosomes with lysosomes (available in phagosomes living microbes such a merger often do not stand up and die). Secondly, lymphokines increase the activity of NADPH oxidase, which is responsible for the formation in the membranes of phagosomes O2 - and H2O2 - basic microbicidal phagocytic factors.

Ways to start and development of acute and chronic inflammation are fundamentally different: 1. In acute inflammation process starts "from the vessels", while in chronic inflammation - a territory of the connective tissue where macrophages are active.

2. The leading cell acute inflammation - effector - a neutrophil, and chronic inflammation - the activity of macrophages. All other mesenchymal cells (fat, lymphocytes, eosinophils) also contribute to the implementation process, modulating the reactivity of neutrophils and macrophages.

3. Acute inflammation of finishes quickly, in a matter of days, unless there are complications in the form of purulent cavities (abscess).

4. Chronic inflammation can not end quickly for the following reasons:

- Firstly, the macrophages in inflammation have a long life cycle, which is calculated in weeks, months or even years. First, in step nucleation granuloma come in fresh blood monocytes, lymphocytes - blood and lymph. They still do not have a sufficiently high microbicidal activity. Then granuloma gradually maturing, and it accumulates differentiated macrophages, actively absorb germs. Finally, at the final stage, the number of long-standing granuloma actively phagocytic cells is reduced, but increased the percentage of relatively inert in terms of phagocytosis of epithelioid and giant multinucleated cells;

- Secondly, any granuloma - it is not "frozen" education. It is constantly followed by a stream of ever new monocytes from bone marrow blood. If many granulomas activated macrophages, cells will exceed the inflow outflow granuloma. The fact that irritated macrophages strongly develop special hematopoietins. They stimulate the production of phagocytes in the bone marrow. Among them is the colony stimulating factor Metcalf. So while angry macrophages "work", the balance will shift in the direction of the inflow cells to infiltrate, and its resolution is not possible.

If the macrophages secrete a lot bio-oxidant in their environment, they can not only sanitize the center, but also damage the body's own cells. When overproduction of H_2O_2 and O_2 of these factors can escape from the phagosome in the cytosol of macrophages and lead to his death. In order to prevent such a situation, there is a system in macrophages emergency neutralize excess bio-oxidant. It includes enzymes: catalase, glutathione peroxidase and glutathione reductase. In particular, under the action of glutathione reductase carried neutralization of hydrogen peroxide in the reaction H_2O_2 + 2 GH – G-G + $2H_2O$ wherein g - glutathione. The enzyme superoxide dismutase neutralize superoxide anion radical (O_2 -) O_2 reaction - + O_2 - + 2H + - H_2O_2 + O_2. When the antioxidant defense system does not work, it leads to persistent inflammation.

Chronic inflammation can last for a lifetime. Periodically it is exacerbated when a hearth receives fresh neutrophils and macrophages with high pro-inflammatory activity. The focus of mononuclear infiltration is the destruction of connective tissue. In response to this is the proliferation of fibrous structures. Ultimately sclerosis may develop a partial or total shutdown of specialized organ functions. This contributes to the accumulation of a particular class of granuloma macrophages secreting fibroblast stimulation factors. With this situation the doctors have to meet with cirrhosis of the liver after viral hepatitis, chronic pneumonia, chronic glomerulonephritis, and other chronic inflammatory diseases of the proceeding.

Local signs of inflammation

The main signs of inflammation are known for a long time. Another Roman scholar lexicographer A. Celsus in his treatise "On Medicine" has identified the following main local signs of inflammation: redness (rubor), swelling (tumor), heat (color) and pain (dolor). The Roman physician and naturalist K.Galen to four signs of inflammation, dedicated A.Tselsom added a fifth - impaired function (functio laesa). Although these symptoms characteristic of acute inflammation of the outer sheets have been known for over 2,000 years, they have not lost their relevance today. Over time, I have only their explanation. These five features have stood the test of time and got a modern and pathophysiological characteristic histopathology.

Redness - striking clinical sign of inflammation, is associated with the expansion of the arterioles, the development of arterial hyperemia and "arterialization" venous blood in the inflammation.

Swelling in inflammation due to an increase in blood supply to the tissue, the formation of infiltration, due to the development of exudation and edema, swelling of the tissue elements.

Heat, heat sore area develops as a result of the strengthened inflow of warm arterial blood, and also as a result of the activation of the metabolism, increase heat production and heat loss in the inflammation.

Pain - is the result of irritation of sensory nerve endings of various biologically active substances (histamine, serotonin, bradykinin, prostaglandins, and some others.), The pH of the internal environment of a shift to the acid side, the mechanical compression of the receptors, the nerve fibers inflammatory edema.

Violation of the functions on the basis of inflammation occurs, as a rule always; sometimes it may be limited to the affected tissue disorder functions, but most suffer from the whole body, especially when the inflammation occurs in the vital organs. Violation of the inflamed organ function due to structural damage, the development of pain, disorders of the neuroendocrine regulation of it.

In chronic inflammation, and inflammation of internal organs, some of these symptoms may be absent.

General manifestations of inflammation

Common manifestations of inflammation due to the influence of the focus of the process is mainly inflammatory mediators.

Fever is a result of endogenous pyrogens, particularly IL-1 released by activated leukocytes hearth inflammation and peripheral blood at the center of thermoregulation.

Rapid metabolism is the result of enhanced secretion of catabolic hormones, in particular under the influence monokines, and may be secondary to fever. In this case, the blood was increased glucose, globulins, residual nitrogen.

Increased ESR reflects the absolute or relative prevalence of plasma albumin globulins of that is due to increased production by hepatocytes under the influence of monokine "acute phase proteins" or advanced loss of albumin with exudation. The preponderance of coarse proteins in plasma reduces the negative charge of red blood cells and thus their mutual repulsion. This increases the agglutination of erythrocytes and consequently their deposition.

Changes in the immune properties of the organism, manifested, in particular, high resistance to repeated impact flogogen, especially infection, caused by the formation during inflammation of cellular and humoral immunity. In this play an important role lymphoid cells are the source of inflammation, such as B-lymphocytes that turn into plasma cells - producers of antibodies. Inflammation produces immune reactivity ("immunity through illness").

Especially big changes are observed in the blood system, reflecting its role as the primary effector system of inflammation. In addition to the emigration of leukocytes into the hearth, the reaction of the blood system in inflammation include a number of changes in the hematopoietic tissue

and peripheral blood: 1) the initial transient decrease in the number of circulating leukocytes (transient leukopenia), due to their marginal and emigration; 2) reduction in the number of mature and immature granulocytes and monocytes in the bone marrow as a result of their enhanced elution

into blood, which is provided reflex and possibly humoral blood flow acceleration in the bone marrow. When the number of leukocytes in the blood received from the bone marrow exceeds the number of emigrants in the inflammatory focus, develop leukocytosis; 3) subsequent recovery of immature and mature granulocytes and monocytes in the bone marrow, indicating activation of hematopoiesis; 4) increase (compared to the original) and the total number of individual germs myelokaryocytes cell hematopoiesis in bone marrow, indicating its development hyperplasia. All this ensures the development and maintenance of long-leukocyte infiltration of inflammatory focus.

Activation of hematopoiesis in inflammation due to enhanced generation of stimulated leukocytes source of inflammation and blood hematopoietic substances - growth factors, interleukins, and others that are self-sustaining mechanism for initiating link leukocyte infiltration of inflammatory focus. The self-regulation of infiltration are essential lysosomal enzymes, reactive oxygen species, eicosanoids.

For acute inflammation is characterized by leukocytosis with a left shift (increase in the number of younger, stab and young neutrophils due to involvement of bone marrow reserve and activate hematopoiesis) and monocytosis to chronic inflammation - monocytic leukocytosis and lymphocytosis.

In the event of common phenomena in inflammation are important, in addition to the humoral, and reflex influences from the hearth. This is evidenced, for example, increased Goltz reflex in the frog (slowing of heart rate with gentle effleurage stomach) with the inflammation of the abdominal cavity.

Role of a reactivity in inflammation

Origin, development, course and outcome of inflammation depend on the reactivity of the organism, which, in turn, is primarily determined by the functional state of the higher regulatory systems - the nervous, endocrine and immune.

The role of the nervous system. Involvement of the nervous system in the pathogenesis of inflammation became apparent through research II Mechnikov in comparative pathology of inflammation, which showed that the more complex the organism, the more differentiated his nervous system, the brighter and more fully expressed in the inflammatory response. In the future, the essential role of reflex mechanisms in the genesis and development of inflammation has been established. Pre-anesthesia tissue at the application site flogogen postpones and reduces the inflammatory response. Anatomical or chemical break the afferent part of the reflex arc during inflammation weakens its further development. As mentioned, the short-term ischemia and arterial hyperemia in inflammation have a reflex nature. On the role of reflex reactions shown by the data of clinical observation that inflammation may develop spontaneously on the symmetric parts of the body.

On the value of the higher parts of the central nervous system indicate developmental delay and attenuation of inflammation on a background of anesthesia or during hibernation. Known ability to play a conditioned reflex inflammation and leukocytosis: the action of a conditioned stimulus (heat or scratching the skin of the abdomen) after the establishment of a conditioned reflex with flogogen (intraperitoneal administration of killed staphylococci) as the unconditioned stimulus.

On the role of the lower parts of the central nervous system development data indicate extensive inflammatory processes in the skin and mucous membranes in chronic damage to the thalamic region.

It is believed that this is due to a violation of the nervous tissue trophism and thus decreasing their resistance to noxious agents.

A significant influence on the development of inflammation has the autonomic nervous system. On desympathic rabbit ear inflammation occurs more rapidly, but also ends faster. Conversely, stimulation of the sympathetic nerves inhibits the development of inflammation. Acetylcholine causes vasodilation and has a value in the development of arterial hyperemia in inflammation, increases emigration. Norepinephrine causes short-term ischemia, inhibits the growth of vascular permeability and emigration. Thus, the parasympathetic nervous system exerts a pro-inflammatory effect, and sympathetic - an anti-inflammatory.

The role of the endocrine system. In relation to inflammation hormones can be divided into pro- and anti-inflammatory. The former include somatotropin, mineralocorticoid, thyroid hormones, insulin, to the second - corticotropin, glucocorticoids, sex hormones.

The role of the immune system. In the immunized organism as a result of increased resistance to the harmful agent is characterized by a reduced intensity of inflammation and ends faster. With reduced immunological reactivity (immunological deficiency - hereditary and acquired immunodeficiencies) observed prolonged sluggish, often recurrent and repeated inflammation. With increased immunological reactivity (allergic) inflammation occurs more rapidly, with a predominance of alterative effects, up to necrosis.

Effectors nervous, endocrine and immune systems - neurotransmitters, neuropeptides, hormones and lymphokines performed as a direct regulatory effect on tissue and blood vessels, hemodialysis and lymphopoiesis and mediated by other mediators of inflammation, where they modulate release through specific cell membrane receptors and changes concentration of cyclic nucleotides in the cells.

The inflammation can be normergic, hyperergic and hyperergic depending on the reactivity of the organism.

Normergic inflammation - usually occurs inflammation, inflammation of the normal body.

Hyperergic inflammation - inflammation of the rapidly flowing, inflammation in the sensitized body. Classic examples are the phenomenon of Arthus reaction Pirke et al. It is characterized by a predominance of alteration phenomena.

Hyperergic inflammation - weakly expressed or sluggish current inflammation. First observed with increased resistance to the stimulus, such as the immunized organism, and is characterized by a reduced intensity, and faster completion (positive hyperergic); the second - at a reduced total and immunological reactivity (immunodeficiencies, starvation, cancer, diabetes, and others.) and has a weak dynamics, protracted, and delayed elimination flogogen tissue damaged them permission response (negative hyperergic).

The value in the pathogenesis of inflammatory reactivity allowed to consider it as a general response of the body to the local damage.

TYPES OF INFLAMMATION

By the nature of vascular tissue reaction distinguish alterative, exudative-infiltrative and proliferative inflammation. View inflammation depends on the reactivity of the organism, the localization process, the type, strength and duration of action flogogen.

Alterative inflammation is characterized by extreme severity events dystrophy (up to necrobiosis and necrosis), and thus, their prevalence of exudative-infiltrative and proliferative. Most often alterative inflammation occurs in the parenchymal organs and tissues (myocardium, liver, kidney, skeletal muscle) in infections and intoxications, so also called parenchymal. When expressed

necrobiotic changes alterative called necrotizing inflammation, such as immune complex allergic inflammation (experimental Arthus phenomenon and arthus similar reactions in humans).

Exudative-infiltrative inflammation is characterized by a predominance of circulatory disorders with exudation and emigration of alteration and proliferation. Depending on the nature of fluid it may be serous, fibrinous, purulent, putrid, hemorrhagic and mixed.

Proliferative or productive, characterized by inflammation of the dominance of cell division and proliferation of connective tissue. Alterative and exudative-infiltrative effects are mild. Proliferative inflammation characteristic of chronic diseases - Tuberculosis, syphilis, leprosy, rheumatism, etc., for acute infectious granulomatous processes - typhoid and typhus typhus, vasculitis of varying etiology, etc., for long-term skin irritation by chemicals.. It is observed around the animal parasites (Trichinella, cysticercus, etc.) and foreign bodies.

Course of inflammation

The flow of inflammation is determined by the reactivity of the organism, the type, strength and duration of action flogogen. Distinguish acute under acute and chronic inflammation.

Acute inflammation is characterized by fairly severe intensity, and relatively short duration. It is believed that clinically it is completed within two weeks. In view of the reaction it is usually exudative-infiltrative. The role of the main effectors in its pathogenesis play polymorphonuclear leukocytes.

Chronic inflammation is characterized by low intensity and long duration - from several months to many years and decades. By the nature of vascular tissue reaction it is often the proliferative. The leading role in its pathogenesis play monocytes, macrophages and lymphocytes. Chronic inflammation can be primary or secondary (due to the transition of acute inflammation in chronic). The development of primary chronic inflammation is primarily determined by the properties flogogen (tuberculosis, syphilis, etc.), secondary chronic - especially the reactivity of the organism.

Subacute inflammation occupies an intermediate position. His clinical duration - approximately 3-6 weeks.

Acute inflammation may acquire a prolonged duration, t. E. Become an acute or chronic secondary. Perhaps the fluctuating course of chronic inflammation when periods subsided process alternate with exacerbations. In the period of acute amplified and become predominant exudative phenomena with infiltration of polymorphonuclear leukocytes and even alterative. In the future, to the fore once again go the proliferative effects.

On the whole, the fundamental differences in the mechanisms of common acute and prolonged inflammation is not available (inflammation - a standard process). The difference is that in a protracted process because of altered reactivity of the organism is disturbed the unity of the damage and protection in inflammation and the last character becomes negative hyperergic, proliferative.

OUTCOMES OF INFLAMMATION

The outcome of inflammation depends on its type and flow, location and extent. The possible outcomes of inflammation:

- Almost full restoration of the structure and function (return to normal - restitutio ad integrum). There is an insignificant injury, when there is a restoration of tissue-specific cells.
- The formation of the scar (return to normal with incomplete recovery). There is significant when the defect at the site of inflammation and its replacement by connective tissue. The scar may not affect the functions or lead to violations of functions as a result of: a) an organ or tissue deformation (such as scarring of the heart valves) or b) the enforcement bias (eg, light as a result of the formation of adhesions in the chest cavity in the outcome of pleurisy).
- The death of the body and the whole body - with necrotizing inflammation.

- The death of the body at a certain localization of inflammation - for example, by suffocation due to formation of diphtheritic films on the mucous membrane of the larynx. Threaten a localized inflammation in vital organs.

- The development of inflammatory complications:

3) intake of fluid in the body cavity with the development of, for example, peritonitis in inflammatory processes in the abdominal cavity;

4) the formation of pus with the development of an abscess, cellulitis, empyema, Pius;

5) multiple sclerosis or cirrhosis of the body as a result of diffuse proliferation of connective tissue proliferative inflammation.

6. Transition of acute inflammation in chronic.

The clinical outcome of the inflammation is very important underlying disease, if the occurrence of focus (foci) inflammation associated with it.

Inflammation value for body

In respect of general biological inflammation is an important protective-adaptive reaction formed in the course of evolution as a way to save the cost of the whole organism part of the damage. It is a way of emergency protection of an organism that is used in the case when the body

is unable to cope with the harmful agent by its physiological elimination and there was damage. Inflammation is a kind of biological and mechanical barrier, through which ensured the localization and elimination of flogogen and (or) tissues damaged them and reinstatement or compensation of tissue defects. Biological barrier properties are achieved by adhesion, lysis and killing of bacteria, the degradation of damaged tissue. mechanical barrier function is carried out by deposition of fibrin coagulation of lymph in the hearth, the blockade of the blood and lymph vessels, connective tissue cell reproduction on the border of the damaged and normal tissue (demarcation). This prevents the absorption and spread of germs, toxins, products of disturbed metabolism, and decay.

Inflammatory lesions has not only a barrier, but also drainage function: with the exudate from the blood to leave hearth products impaired metabolism, toxins.

As already indicated, inflammation affects the formation of immunity.

However, the feasibility of inflammation as a protective and adaptive reactions is unconditional only in evolutionary and biological terms. And as a local process at a certain location and extent of inflammation may be accompanied by a common pathological manifestations (toxicity, reactivity change and others.) And even in the normal course may purchase harmful for the body. Furthermore, in connection with altered reactivity in practice frequently downstream unusual forms of inflammation and complications.

Acute phase response.

Acute phase response - this is such a non-specific response of the body system that occurs when the action on the organism pathogenic factor which causes any damage, accompanied by a marked impairment of hemostasis. It is, along with the local inflammatory response a number of complex systemic reactions are due to the activation of protective and regulatory systems of the body.

The etiology of acute-phase response

Pathogenic factors:

6. Infectious: - Bacteria
- Fungi, - Viruses,

7. Noninfectious:
- Acute and chronic diseases of infectious nature,
- Burns,
- Tissue injury,

- Ischemic,
- Damage.

Tissue damage (infection, trauma, autoimmune diseases, tumors, etc.)

↓

Local reactions (inflammation, leukocyte activation, fibroblasts, endothelial and other cells)

↓

Release of mediators (IL-1, IL-6, TNF-alpha, interferon-γ, etc.)

↓

systemic reactions

↓	↓	↓	↓	↓
The nervous system (hypothalamus)	Endocrine system (pituitary gland)	liver	hematopoietic system (bone marrow)	Immune System
↓	↓	↓	↓	↓
Fever	ACTH	Acute phase proteins	leucocytosis, reticulocytosis	activation of lymphocytes

Acute phase response due to the action of bacterial, viral and fungal infections, acute and chronic infectious nature, and burns, injuries, ischemic tissue damage, and other neoplastic growth.

Systemic reactions, which constitute the essence of the acute phase response associated with the synthesis of specific neurotransmitters in the body, which perform the function of pro-inflammatory cytokines. They are secreted by cells involved in the inflammatory response, developing at the site of the primary damage:. Monocytes, macrophages, neutrophils, lymphocytes, microcirculatory vascular endothelial cells, fibroblasts, etc. These mediators released into the bloodstream and the condition for their effects on target cells is the presence on the surface recent relevant receptors. Among the most important mediators of the acute phase response include IL-1, IL-6, tumor necrosis factor (TNF-a).

The spectrum of the target cells as wide as the range of the producer cells. These include hematopoietic cells, nearly all immune cells including monocytes, macrophages and lymphocytes, vascular endothelial cells, hepatocytes, in the case of IL-1 - hypothalamus and pituitary cells, etc.

Provided infiltration of inflammatory cytokines into the bloodstream realized their systemic effects, including stimulation of the manifestations of the acute phase response.

The action of cytokines is preferably considered protective in nature, however, in those cases where a stimulus to their elaboration and activation of target cells is too intense, the effect of the: cytokines may be destructive. This is evident in the development of local tissue damage due to overly intense development of inflammation, and induction of programmed cell death.

Acute phase proteins

The degree of increase content	Name protein
Significant (1000 times or more)	C-reactive protein, serum amyloid A
Moderate (210 times)	α-1-antitrypsin, and -antihimotripsin-1, fibrinogen, haptoglobin
Weak (2 times)	ceruloplasmin, NW component of complement, C1 inactivator complement component

Acute phase response is characterized by a significant increase in serum specific proteins, which are called acute phase proteins. In humans, it is referred to the C-reactive protein, serum amyloid A, fibrinogen, haptoglobin, a-1-antitrypsin, a-1-antichymotrypsin and others - about 30 proteins.

Acute phase proteins involved in the processes that contribute to maintaining homeostasis: in the development of inflammation, phagocytosis foreign particles, neutralize free radicals, inactivation of a host of potentially dangerous tissue enzymes, etc.

When developing acute injury concentration of C-reactive protein and serum amyloid A in the blood increases considerably already after 6-10 hours after initiation of damage.

The concentration of other acute phase proteins including fibrinogen antienzymes and grows more slowly over 24 - 48 hours.

There are proteins, whose content in the serum during the acute phase response is reduced. Such proteins are sometimes called negative acute phase proteins. These include, in particular, albumin and transferrin.

The level of acute phase proteins in the blood is determined, above all, their synthesis and secretion by hepatocytes. The most important role in the regulation of these processes belong to IL-6 and related cytokines, to a lesser extent IL-1, TNF-a, and glucocorticoids.

Perhaps production of various acute phase proteins is controlled by various cytokines. C-reactive protein (CRP) was one of the first identified of acute phase proteins. It was named in connection with the ability to interact in the presence of Ca2 + to the C-polysaccharide of pneumococcus. CRP interacts with the polysaccharide and lipid components of microbial surfaces, especially with phosphorylcholine. At the same time, he can not interact with the somatic cells of the host phosphorylcholine.

C-reactive protein acts as an opsonin because of his relationship with the microorganisms facilitates the absorption of the host phagocytes; activates complement, promoting lysis of bacteria and the development of inflammation; enhances the cytotoxic effect of macrophages for tumor cells; It stimulates the release of cytokines by macrophages.

Serum CRP increases rapidly in the early infectious and noninfectious diseases (1 ug / ml to over 1 mg / ml) and rapidly decreases with recovery. Therefore, CRP is bright enough, although non-specific marker of damage.

Serum amyloid A (SAA) - the other major acute phase protein in humans. It is in serum in conjunction with high-density lipoproteins and causes chemotaxis and adhesion of phagocytes and lymphocytes, promoting inflammation in atherosclerotic vessels.

Continued increase in blood SAA in chronic inflammatory and neoplastic processes predisposes to amyloidosis.

Fibrinogen - protein coagulation; It creates a matrix for wound healing, has anti-inflammatory activity, inhibiting the development of edema.

Ceruloplasmin (polyvalent oxidase) - a protein containing copper protector of cell membranes, the neutralizing activity of superoxide and other radicals produced during inflammation.

Haptoglobin - hemoglobin binds and thus formed complex acts as peroxidase - an enzyme that promotes the oxidation of various organic substances peroxides. Competitively inhibits cathepsin C and cathepsins B and L. limits the utilization of oxygen by pathogenic bacteria.

Inhibitors of enzyme activity - the so-called antienzymes - serum proteins that inhibit proteolytic enzymes in the blood from penetrating the site of inflammation, where they appear as a result of degranulation of leukocytes and cell death of damaged tissues. These include but-1-antitrypsin, which inhibits the action of trypsin, elastase, collagenase, urokinase, chymotrypsin, plasmin, thrombin, renin, leukocyte proteases. Lack of a-1-antitrypsin results in tissue destruction by enzymes in the inflammation leucocytes.

Another known antiferment a-1-antichymotrypsin - has an effect similar to that of a-1-antitrypsin.

Transferrin - protein providing iron transport in blood. In the acute phase response in the plasma content is reduced, which leads to giposidermii. Another reason giposidermii with severe inflammation can be increased iron uptake by macrophages and increase iron binding lactoferrin, which is synthesized and neutrophils in the blood content of which is increased in parallel with an increase of neutrophil content. At the same time with a decrease in the content of transferrin enhanced synthesis of ferritin, which contributes to the transition of labile iron in ferritin and difficult to use supplies of iron. Reduced serum iron prevents the growth of bacteria, but at the same time can contribute to the development of iron deficiency anemia.

Mediators of the acute phase response

Interlepkin-1 (IL-1) - a multi-functional (pleiotropic) cytokine, first discovered as a product of leukocytes, causing fever when administered to animals. He belongs to a family consisting of three structurally related peptides: interleukin-la (IL-1a); interleukin-lp (IL-β) receptor antagonist for IL-1.

The two known IL-1 forms (a and P) - the products of different genes. They differ in their amino acid sequence, but have a similar three-dimensional structure. Interleukins interact with the same receptor, revealing similar biological activity. The main form is a secretory IL-1β.

Interleukin-1 secrete many cells: monocytes, macrophages, endothelial cells, neutrophils, B cells, natural killer cell, fibroblasts, dendritic cells of the skin, kidney mesangial cells, glial cells, neurons. Ability to secrete IL-1 also exhibit some tumor cells.

IL-1 production may be caused by various agents, including microorganisms and their metabolic products: antigens of non-microbial origin, organic and inorganic compounds antigenic origin (e.g., silicon salts, bile acids, uric acid), cytokines (TNF-α, IL-6) active component of complement (C5a), neurohormones (substance P), tobacco glycoproteins, ultraviolet radiation, gamma radiation, hypoxia or hyperoxia, overheating and others.

Interleukin-1 mediates various protective processes in the body that are activated by damage of different tissues. As noted, it is one of the most important mediators of inflammation that develops at the site of damage. When inflammation associated with production of IL-1 increases, it causes a systemic reaction, which makes it important mediator of the acute phase response.

Interleukin-1 stimulates the immune system: activate T-cells and enhances the production of interleukin-yn-2 receptor induces expression of IL-2 antigen on activated T cells. This leads to the rapid proliferation of the appropriate T cell clone. Together with other cytokines activate B cells, promoting their proliferation and differentiation into plasma cells producing antibodies.

This cytokine influences the central nervous system. The appearance in the IL-1 brain causes fever, lethargy, loss of appetite, weakness, decreased interest in things, depression, changes the function of the endocrine system. It activates the axis of the "hypothalamus - pituitary gland - the adrenal glands", causes the release of arginine vasopressin hypothalamus. At the same time it inhibits prolactin secretion, reduces the secretion of gonadotropin and sex steroid hormones. One of the important effects of changes in the functions of the endocrine system under the influence of IL-1 is to revent excessive activation of the immune system.

Interleukin-1 acts as hematopoietins on bone marrow stem cells in the presence of IL-3 and other hematopoietic factors, which leads to leukocytosis and leftward shift to an increase in blood platelets. IL-1 stimulates the secretion of other cytokines involved in the acute phase responses, particularly IL-6 and TNF-a.

There are two types of surface receptors for IL-1 (IL-IP): IL-IP, and type I IL-IP type II, extracellular domains, which are similar, but distinct intracellular. Communication with the IL-1 type I receptor transmits the signal into the cell, and the connection with the IL-1 type II receptor does not result in signal transduction. As a result of type II IL-IP acts as a "trap" for the IL-1, preventing its interaction with a very large number of type I and thus the excessive activation of the receptor target cells.

Much of the IL-1 effect is realized with participation of cyclooxygenase which catalyzes the metabolism of arachidonic acid, leading to the formation of prostaglandins. Blockers cyclooxygenase (acetylsalicylic acid, indomethacin) suppresses fever, loss of appetite, enhanced secretion of ACTH and other effects of IL-1.

There is a complex system of regulation of the potentially damaging effects of IL-1 in the human body. In the blood of healthy people and patients with circulating soluble IL-1 receptors, which are extracellular fragments of IL-1 and II type 1 receptor cytoplasmic. Both soluble receptor binds IL-1 free, thus preventing its interaction with membrane receptors.

Another important element of the system of regulation of action of IL-1 is a natural antagonist of IL-1 receptor. The natural antagonist of IL-1 receptor (IL-1 RA) - the third member of the IL-1 family. The size and structure of its molecules resemble those of IL-1. An antagonist of the IL-1 receptor produces many cells, including ones that secrete IL-1, although the major producers of natural IL-1 RA are likely to hepatocytes, which makes it one of the acute phase proteins. An antagonist of the IL-1 receptor binds to cellular receptors for IL-1, thereby blocking the action of IL-1 on its target cells. The interaction of IL-1 RA receptor is not a signal for the beginning of any intracellular processes, in connection with which it is called pure receptor antagonist. Introduction The antagonist of IL-1 receptor effectively inhibits many IL-1 induced pathological processes: fever, lethargy, hypotension, acute phase protein synthesis in liver, symptoms of septic shock in vivo.

Despite the existence of these mechanisms of deterrence proinflammatory activity of IL-1, under certain circumstances it is secreted in excessive amounts, which causes tissue damage, which may exceed the degree of initial damage. In such cases, the production of IL-1 becomes the determinant of all the further course of the disease. A significant increase in serum IL-1 β is found in septic shock - a clinical syndrome arising in severe bacterial infections. The syndrome is characterized by profound hypotension, fever, increased content of leukocytes in peripheral blood. Many symptoms of septic shock may be reproduced in animals by administration of IL-1. Introduction blocker actions of IL-1 has a beneficial effect in experimental septic shock in animals and in humans with septic shock.

In rheumatoid arthritis - chronic non-bacterial inflammation of the joints - synovial membrane infiltrated by macrophages, lymphocytes, and other chronic inflammatory cells. In the synovial fluid of joints found IL-1, and many of the symptoms of rheumatoid arthritis - leukocyte infiltration of the synovial membrane, the disintegration of the cartilage and remodeling of the bone around the joints - can be replicated in animal experiments by introducing them into the joint IL-1.

Interleukin-1 is one of the main mediators of acute lung injury occurring in acute respiratory distress syndrome adults, which shows sharp massive pulmonary edema and neutrophil infiltration of lung tissue. In bronchial lavage fluid show increased concentration of IL-1.

There is strong evidence for the involvement of IL-1 in tissue injury in inflammatory bowel diseases, kidney, pancreas death in β-cells in insulin-dependent diabetes mellitus, the development of atherosclerosis and the pathogenesis of many other diseases. The data that the IL-1 contributes to the progression of myeloid leukemia.

Interleukin-6 (IL-6) - multifunctional (pleiotropic) cytokine first identified as a T cell-secreted factor causing terminal differentiation of B cells into plasma cells producing antibodies. The chemical structure is a protein molecular weight of about 26,000.

Among the IL-6-producing cells are macrophages, fibroblasts, vascular endothelial cells, epithelial cells, monocytes, T-cells, keratinocytes skin cells of the endocrine glands, glial cells and brain neurons in discrete regions.

Stimulants IL-6 synthesis include viruses, bacteria, endotoxins, lipopolysaccharides, mushroom, proinflammatory cytokines IL-1 and TNF-a. IL-6 also secrete many forms of tumor cells (osteosarcoma cell carcinoma of the bladder, cervix, myxoma, glioblastoma). Unlike normal cells, tumor cells produce IL-6 continuously without outside stimulation.

Interleukin-6 is a major stimulator of the synthesis and secretion of liver hepatocytes acute phase proteins. In addition, it activates the axis "hypothalamic - pituitary - adrenal", causing secretion of corticotropin-releasing factor neurons of the hypothalamus and directly acting on the anterior pituitary cells. Like IL-1, IL-6 mediates the febrile response to endotoxin, it stimulates proliferation of white blood cells in bone marrow.

Interleukin-6 is required for the ultimate differentiation of activated B cells into plasma cells producing antibodies, it enhances the production of certain classes of immunoglobulins mature plasma cells, stimulates the proliferation and differentiation of T cells, enhances IL-2 production by mature T-cells.

IL-6 belongs to a family of hematopoietic cytokines. It has the properties of a growth factor and differentiation of multipotent stem cells and stimulates the growth of granulocytes and macrophages.

Although the primary role of IL-6 is the activation of processes of restoration of disturbed homeostasis and its overproduction contributes to tissue damage. Thus, there is a direct correlation between the degree of increase in IL-6 and the progression of the autoimmune response. IL-6 promotes inflammatory joint damage in rheumatoid arthritis. Prolonged elevation of IL-6 in blood could be the cause of activation of osteoclasts destroying bone.

The third key mediator of the acute phase response - tumor necrosis factor (TNF-a) - was first identified as an agent capable of killing tumor cells in vitro and cause hemorrhagic necrosis of transplanted tumors in mice in vivo. This turned out to be the agent responsible for cachexia, evolving with severe chronic diseases, which gave him the second name "cachectin".

TNF-producing cells, and are primarily macrophages, and in addition, T -, B-cells, T-killer cells, neutrophils, eosinophils, astrocytes, fat cells.

TNF-a production can be caused by bacterial toxins (LPS, enterotoxin), viruses, mycobacteria, fungi, parasites, activated complement components, complex "antigen - antibody", cytokines (IL-1, IL-6, GM-CSF).

Tumor necrosis factor has a potent pro-inflammatory action, which is found primarily in the areas of its release. It activates white blood cells, induces expression of adhesion molecules on the membrane of the endothelial cells of blood vessels microcirculation, thus contributing to the migration of leukocytes from the blood in extracellular matrix; It stimulates the secretion of leukocyte reactive oxygen metabolites; involved in inflammation stimulates secretion inflammatory cytokines cells, including IL-1, IL-8, IL-6, γ-interferon. During the healing of wounds and TNF promotes fibroblast proliferation and stimulates angiogenesis.

Tumor necrosis factor enhances T cell proliferation, proliferation and differentiation of B-cells stimulates the growth of NK cells, increasing their cytotoxicity. TNF-a - one of the important defense factors from intracellular pathogens, it has antiviral activity and inhibits the growth of or causes hemorrhagic necrosis of tumors in vivo, is cytotoxic to many tumor lines in vitro cells.

While all of these actions of TNF-a focus on restoration of disturbed homeostasis, overproduction of his appeals system toxic effects, the nature of which depends on the degree and duration of TNF-alpha in the blood rise. Among the toxic effects caused by the rapid and significant increase in TNF-a, to be primarily called hemodynamic disorders characterized by a reduction in myocardial contractility, cardiac output falling, decrease venous return. TNF-a in a high concentration causes an increase in capillary permeability diffuse. Disorders causing hemodynamic shock and multiple organ failure functions. TNF-a excess gives anticoagulant properties of vascular endothelium, which contributes to disseminated intravascular coagulation. And hyperproduction of TNF can cause and other life-threatening disorders including acute adult respiratory distress syndrome, multiple necrosis in the gastrointestinal tract, renal tubular epithelial necrosis and hemorrhages in the adrenal glands.

Increasing the concentration of TNF-a to a lesser extent, but for a longer period causes anorexia, fever, cachexia due to enhanced protein catabolism and disappearance of fat reserves, dehydration, synthesis of acute phase proteins in liver and insulin resistance.

Both acute and chronic effects of TNF-a are due to its direct effect on target cells and action of other substances which release TNF-alpha stimulates. Thus, the acute toxic effects of high TNF-a concentration is associated with its direct cytotoxic effect on many cells, including cells of the contractile myocardium, vascular smooth muscle and vascular endothelial cells, and release of biologically active substances such as catecholamines, glucagon, ACTH, cortisol, IL-1, IL-6, γ-interferon, platelet activating factor, eicosanoids. The occurrence of fever and anorexia due to the direct action of TNF-α in the hypothalamic neurons. Direct effects of TNF-α on the adipose tissue cell causes inhibition of lipogenic enzymes lipoprotein lipase in particular, leading to a gradual disappearance of adipose tissue. TNF-α action on muscles causes muscle insulin resistance, breakdown of muscle protein reduction potential of the membrane of muscle fibers, which facilitates the transition of sodium and water into the water of myocytes and reduce the extracellular space of tissues dehydration.

There are two types of receptors for TNF-a, which are present in all cell types with the exception of erythrocytes. Type I receptors have a molecular weight of 55,000, molecular weight receptor type II - 75 000. Many, especially cytotoxic, effects of TNF-a on various cell mediated type I receptors (Rts55). Participation type II receptor (Rts75) in cytotoxicity may be reduced to the fact that they bind TNF-alpha and "pass" then it Rts55, which provide signal transmission. Both types of receptors involved in various ways in the implementation of TNF-induced apoptosis and cell.

The cytotoxic effects of TNF-a is amplified in the presence of protein synthesis inhibitors. It is believed that many of the cells produce proteins that neutralize TNF-a or "resist" its cytotoxic effect. High cytotoxicity of TNF-a to tumor cells may be due to the fact that tumor cells do not produce such proteins. The serum and urine of patients with tumors, AIDS, sepsis found fragments of the extracellular domains of both types of receptors, known as TNF binding proteins. TNF-a concentration of these proteins in blood significantly increased in conditions of excessive production. Proteins bind to TNF-a in the extracellular fluid, thereby preventing the interaction of TNF-alpha to cytoplasmic receptors and preventing the cytotoxic effect of TNF-a cells. Despite the fact that the molar concentration of TNF-binding proteins, typically several orders of magnitude greater than the molar concentration of TNF-a, it is not enough to prevent the toxic effect of TNF-a in septic shock, and meningitis.

Manifestations of acute-phase response

To answer the acute phase is characterized by disturbances due to involvement in the response of the nervous, endocrine, immune and hematopoietic systems, which include:

4. Fever;
5. Drowsiness;
6. Loss of appetite (anorexia);
7. Indifference to the environment;
8. Muscle pain (myalgia) and joints (arthralgia);
9. Neutrophilic leukocytosis with a shift to the left;
10. Acceleration of ESR;
11. Activation of phagocytosis (increased oxygen metabolism, absorption and bactericidal activity of neutrophils, moocytes, macrophages);
8. Changes in the concentration and the ratio of whey proteins - increase in acute phase proteins, reduction of albumin and transferrin;
9. Activation of the complement system;
10. Activation of the blood clotting system; increase in serum several hormones (adrenocorticotropic hormone (ACTH), vasopressin);
11. Negative nitrogen balance;
12. Change in serum microelements (reduced levels of iron and zinc, increased copper).

Fever

Fever - total non-specific response of the body, in most cases developing in response to a hit in the body and / or the formation of there pies. An important manifestation of fever is a fever, irrespective on the ambient temperature. Fever differs from other hyperthermic state of conservation thermoregulatory mechanisms at all stages of its development.

Fever - a typical thermoregulatory responses of the body to the action of the pyrogenic factor; characterized by the dynamic rearrangement of a thermoregulation system function; It manifested a temporary increase in body temperature above normal.

Etiology

The cause of fever - pyrogen. On the criterion of origin distinguish infectious and noninfectious pyrogen.

2. Infectious - Viruses
- Single- and multi-celled parasites - Mushrooms
- Rickettsia - Bacteria

3. Noninfectious
2) Proteins and protein-containing substances
3) Lipids and fatty substances
4) Steroid substance
5) Nucleoproteins

Pyrogens infectious

Pyrogens infectious origin are the most common cause of fever. It is essential that feverish reaction does not trigger these pyrogens (called the primary), and formed in the body under the influence of their secondary (true) pyrogens secreted by different cells (mainly macrophages and neutrophils). Attributed to infectious pyrogenic lipopolysaccharide, lipoteichoic acid, as well as endo- and exotoxins that act as superantigens.

Lipopolysaccharide

The most pyrogenicity possess lipopolysaccharide (LPS, endotoxin). LPS included in the membranes of microbes mainly Gram. Of the three components of LPS - lipid A, protein and polysaccharide - peculiar pyrogenic action lipid A. Microbial pyrogen thermostable, has low toxicity and has no group specificity. Pyrogenic, leading to feverish reaction, not inherent toxicity and pathogenicity. The last two qualities are determined by other (non-pyrogenic) components of microbes. Thus, highly cholera, tetanus, botulism does not have significant pyrogenic property. Pyrogenic property lipid A is used in medicine for therapeutic purposes in the application of pharmacological agents pyrogenal derived from individual bacterial membranes.

Lipoteichoic acid

Gram-positive bacteria contain lipoteichoic acid and peptidoglycan having pyrogenic property.

Superantigens

Numerous endo- and exotoxins staphylococci and streptococci act as superantigens - receptor polyclonal activators of T lymphocytes with subsequent activation of a multiple effects, including the release from macrophages and neutrophils of various cytokines (including secondary pyrogens).

Noninfections pyrogens

Pyrogens noninfectious origin also can cause fever. According to the structure, they often are proteins, fats, at least - the nucleoprotein or nucleic acids, steroid substances. Parenteral administration of a sterile protein-and / or fat-containing substances (whole blood, serum, plasma, vaccines, Ig, lipid emulsions), accompanied by the development of fever. In addition, more or less marked febrile response is always observed under aseptic trauma, necrosis of the organs and tissues (myocardial infarction, lung, spleen, stroke, tumors and other decay.), Hemolysis, non-infectious

inflammation, allergic reactions. When all of these conditions in the body are released non-infectious pyrogen.

Primary and secondary pyrogens

Once in the body or in the formation of the above it infectious and/or non-infectious pyrogenic agents in the blood within 30-70 minutes increases the content of peptides with pyrogenic activity in very low dose. These substances are formed primarily in phagocytic leukocytes (granulocytes and agranulocytes: neutrophils, monocytes / macrophages, and lymphocytes, even though they fewer). Pyrogenic agents indirectly induce the expression of genes encoding the synthesis of cytokines.

- Ingested or formed in it pyrogenic substances (LPS, lipid A, capsules microorganisms, protein-and fat-containing substances, as well as some other compounds) designated as the primary pyrogen.
- Formed in leukocytes cytokines (leucokine) called secondary, true, or leukocyte pyrogens.

Primary pyrogen (fever cause)
↓
Leukocyte pyrogenic polypeptides (secondary pyrogen):
IL-1, IL-6, TNF, gamma-interferon (causes fever)
↓
The neurons of the hypothalamic thermoregulatory center: the formation of PGE2, cAMP
↓
Increased sensitivity of cold receptors of the hypothalamus
↓
Raising "setpoint" thermoregulatory center
↓
Activation of heat mechanisms and
Reduction in the efficiency of heat transfer mechanisms
↓
Increased body temperature

Leukocyte pyrogens

Leukocyte pyrogens are a class of cytokines that intercellular information exchange. Among the large number of cytokines are just a few have a high (although nonspecific) pyrogenic activity. Among pyrogenic include IL-1 (previously referred to as "endogenous pyrogen"), IL-6, TNF, IFN-y.

Pyrogenic cytokines have no species specificity and heat labile (unlike infectious pyrogen lipid A). Repeated formation in the body (or repeated parenteral administration it) give the same effect as the first (i.e., they do not cause formation of tolerance to them, which also differentiates them from bacterial pyrogen).

In this way, Pies - enter the body and / or formed in himself; stimulate the formation of real - leukocyte pyrogens, which cause a feverish reaction.

MECHANISMS OF FEVER

The feverish reaction - a dynamic and stage process. On the criterion of changes in body temperature are three stages of fever:

I. rise of temperature,

II. state at an elevated temperature level,

III. reduce the temperature to normal range values.

I. Stage rise in body temperature

Stage rise in body temperature (stage I, st. Incrementi) is characterized by the accumulation in the body of the additional amount of heat due to the predominance of heat on the heat dissipation.

2 Pyrogenic cytokines are synthesized by leukocytes penetrate the blood-brain barrier and in the preoptic area of the anterior hypothalamus interact with receptors of nerve cells thermoregulatory center. As a result, membrane-bound phospholipase A2 is activated and switched metabolic cascade of arachidonic acid.
3 In the center of thermoregulatory neurons significantly increased the activity of cyclooxygenase. The result is an increase in the concentration of PGE2 in neurons.
4 PGE2 Education - one of the key components of a fever. The argument for this is the fact prevent the synthesis of PGE2 and as a result - of febrile reactions with cyclooxygenase inhibiting activity nonsteroidal anti inflammatory drugs (NSAIDs, such as aspirin, diclofenac sodium, etc.).
5 PGE2 activates adenylate cyclase, which catalyzes the formation of neurons cyclic 3', 5'-adenosine monophosphate (cAMP). This, in turn, increases the activity of cAMP-dependent protein kinases and other enzymes.
6 Evolving concerning change in neurons metabolism reduces the excitability threshold cold receptors (i.e., to increase their sensitivity).
7 This is normal blood temperature is perceived as reduced: cold sensitivity impulses of neurons in the address of the posterior hypothalamus significantly increased effector neurons. In this regard, the so-called thermal installation thermoregulation center point rises.

The changes described above are central to the development of the mechanism of phase I of fever. Later joined by peripheral mechanisms.

Since the shift "set point" the efficiency of heat production mechanisms dominates the efficiency of heat transfer processes.

Increasing the level of "set-point" center of thermoregulation leads to the activation of heat and reduce the efficiency of heat transfer mechanisms mechanisms.

1. Activation mechanisms of heat stimulates the "contractile" thermogenesis (the development of muscle tremors and increase in muscle tension) and "shivering" metabolic thermogenesis (metabolic activation of exothermic reactions).
2. Reduced heat transfer efficiency mechanisms reduces arteriolar lumen skin and reducing sweating.

All these mechanisms lead to an increase in body temperature.

Heat irradiation

Heat dissipation is reduced as a result of the activation (under the influence of the efferent impulses from cold sensitivity thermoregulatory center neurons) neuronal nuclei sympathetic-adrenal system, located in the posterior hypothalamus.

3. Increased sympathetic-adrenal effects leads to generalized arteriolar narrowing of the lumen of the skin and subcutaneous tissue, a reduction in the blood supply, which greatly reduces the amount of heat the body. In this regard, pale skin (indication of its ischemia), and the skin temperature is significantly reduced.
4. Reduced skin temperature causes an increase in the afferent impulses from it of cold thermal receptors in the neurons of thermoregulatory center, as well as the reticular formation, especially the midbrain.

Thermogenesis

- Activation of the structures of the reticular formation of the brain stem stimulates contractile muscle thermogenesis in connection with the excitation of γ- and α-motor neurons of the spinal cord. The last cause tonic tension of skeletal muscles, known as thermoregulatory myotonic condition. This is followed by the activation of the exothermic metabolism in muscle, coupled with an increase in heat generation and body temperature.

- Increasing efferent impulses of neurons of the posterior hypothalamus and the reticular formation of the brain stem causes the timing contractions of individual muscle bundles of skeletal muscle (including chewing, which is accompanied by the phenomenon of "knocking teeth"), which is

manifested as muscle tremors. Tremors provides intensive formation of heat and fever. This is explained by the fact that the muscle trembling (not combined with the performance of external work) a significant part of the energy generated by the oxidation of substrates, is released as heat.

Contractile thermogenesis

The so-called contractile thermogenesis thermoregulatory including myotonic muscular condition and skeletal muscle tremor, is one of the main mechanisms of heat in the body and increase the body temperature in fever. Proof of this is that the pharmacological blockade of the contractile thermogenesis (e.g., via a muscle relaxant) increases latency and reduces the febrile response (but not eliminate) fever.

Shivering thermogenesis

Shivering thermogenesis is another important mechanism of heat in fever. The reasons: the activation of the sympathetic effects on the metabolic processes and increase the level of thyroid hormones in the blood.

Contractile thermogenesis dominates the initial stage I of fever, and later gradually increase the proportion of non-shivering heat production.

1. The mechanism of fever on the stage I rush down to one of three options.

4. The most common is the simultaneous increase in the efficiency of heat production and heat limiting mechanism. Body temperature thus increases very rapidly.

5. In another embodiment, the heat production increases against the backdrop of preserving the effectiveness of heat transfer processes. Body temperature is therefore increased, but less intensively than in the first case.

6. In the third case, the body temperature may increase mainly due to a substantial limitation of heat transfer with less increase in heat production. Body temperature in this case will also increase less rapidly than in the first.

2. Ambient temperature has little influence on the development of fever and body temperature dynamics. The experiment shows that the presence of the organism febrile (fever pathogen when administered) under the ambient temperature, equal to a 43 ° C and 29 ° C, characterized by stereotypical phasic dynamics. Hence an important conclusion:

With the development of fever, thermoregulatory system of the body does not get upset. It dynamically rearranged, activated and operates at a higher functional level.

II. Stage standing body temperature at an elevated level

Stage standing body temperature at an elevated level (stage II, st. Fastigii) is characterized by the relative balance of heat production and heat. However, the balance of these two processes is achieved at a level significantly exceeding until fever. It is this and maintains body temperature at an elevated (compared to until fever period) level: the intense heat production is balanced by an equivalent heat output.

Such a state of thermal balance brings a new level of thermoregulation system functioning:

5. Increase in the activity of heat thermoreceptors preoptic area of the anterior hypothalamus, causes an increase in blood temperature;

6. Activation of the peripheral temperature thermal sensors of the internal organs. In connection with this increased level of adrenergic influences balanced by increasing cholinergic effects. The result of these changes is to reduce the efficiency of heat production processes and increase the heat transfer reactions.

The relative dominance of the heat output processes is achieved through:

7. Expansion of the arterioles of the skin and subcutaneous tissue with the development of arterial hyperemia;

6. Reduce the metabolic rate and as a consequence - of heat production in the body;

7. Increased sweating.

Trends in body temperature between patients with fever of step II is different. This is defined as the duration and degree of temperature rise. At the same time duration and the dynamics of infectious fever are mainly determined by the characteristics of the microorganism, and the amount of increase in body temperature - generally properties of the microorganism.

The duration and the dynamics of febrile reactions are directly dependent on the duration and dynamics of the production of pyrogenic polypeptides under the influence of infectious pyrogens. In addition, the temperature dynamics of its daily fluctuations is determined: as normal, it is maximal at 17-19 hours and a minimum of 4-6 hours.

The temperature curve

The aggregate daily and phasic dynamics is designated as the temperature curve at a fever. When febrile reactions may occur more typical (though to some extent peculiar in each patient) varieties of the temperature curve.

Constant. When it diurnal fluctuations in body temperature range does not exceed 1 ° C. This type of curve is frequently seen in patients with lobar pneumonia or typhoid fever.

Remitting. This type of curve is characterized by daily fluctuations of temperature by more than 1 ° C, but no return to the normal range and is often observed in viral diseases.

Laxative, or intermittent. body temperature variations during the day reach 1-2 ° C, it can moreover be normalized for several hours, followed by its increase. This type of temperature curve are often registered with abscesses of the lungs, liver, purulent infection, tuberculosis.

Depleted, or hectic. This type of curve is characterized by repeated rises in temperature during the day by more than 2-3 ° C with its subsequent rapid declines. This pattern often observed in sepsis. There are some other types of temperature curves.

Given that the temperature in infectious fever curve heavily depends on the characteristics of the microorganism, identification of its type may be of diagnostic value. However, carrying out antimicrobial therapy significantly alters the classic pattern of curves.

The degree of increase in body temperature during fever both infectious and non-infectious origin is determined mainly by the state of reactivity. Specifically, this is determined by the different options:

7. The number of formed pyrogenic cytokines;
8. The sensitivity of the receptors to them;
9. Reactive properties of organs and physiological systems involved in the processes of heat production and heat.

However, we must remember that the individual properties of microorganisms (eg, the ability to uncoupling of oxidative phosphorylation, direct activation or inhibition simpato- and cholinergic systems, increased vascular permeability, and some others) are also able to significantly influence the extent of rise in body temperature.

When fever distinguish several degrees of fever:

10. Weak or low-grade (from normal to 38 ° C);
11. Moderate, or febrile (range 38-39 ° C);
12. High or pyretic (39-41 ° C);
13. Excessive or hyperpyretic (above 41 ° C).

III. Step reduce body temperature to normal

Stage reduce body temperature to a normal range of values (stage III fever, st. Decrementi) is characterized by a gradual decrease in leukocyte production of pyrogenic cytokines.

Cause: The termination of the primary pie, that is due to the destruction of microorganisms and / or noninfections pyrogenic substances.

onsequences: the reduction and / or activity of phospholipase A2, cyclooxygenase, PGE2, cAMP in neurons of the anterior hypothalamus, as well as raising the threshold of excitability of cold receptors and, consequently, reducing their sensitivity. As a result, "adjusting the temperature point" thermoregulatory center is reduced.

Variations reduction temperature in step III fever:

6. Gradual, logical or (more often).
7. Fast, critical or (less often).

Metabolism in fever

The development of fever accompanied by a number of regular changes in metabolism.

Basal metabolism

Basal metabolic rate increases due to the activation of the sympathetic-adrenal and hypothalamic-pituitary-adrenal system, release into the blood iodine thyroid hormone metabolism and temperature stimulation. These processes lead to a generalized intensification and acceleration of the individual to the predominant - limiting - metabolic units. This, on the one hand, provides energy substrates and increased metabolic functioning of several organs and physiological systems, and on the other - contributes to body temperature. Phase I of fever increase in basal metabolism increases the body temperature at 10 - 20% (the rest is the result of reducing the heat loss due to skin vasoconstriction and the same time - increasing the contractile and metabolic thermogenesis). In stage III fever basal metabolic rate decreases.

Carbohydrate metabolism

Carbohydrate metabolism is characterized by a significant activation of glycogenolysis and glycolysis. Decay products of high carbohydrate used in activated oxidative processes. This is evidenced by a regular increase in respiratory rate. However, activation of glucose oxidation is combined with its low energy efficiency. This greatly promotes the disintegration of lipids.

<table>
<tr><td colspan="6">Fever</td></tr>
<tr><td colspan="2">Activation of the hypothalamic-pituitary-adrenal axis</td><td colspan="2">activation sympathetic-adrenal system</td><td>activation thyroid system</td><td>Thermal stimulation of metabolism</td></tr>
<tr><td>Accumulation in the tissues of Na +, Ca2 +, CI-, and others</td><td>Increased basal metabolic</td><td>stimulation of glycogenolysis and glucose oxidation</td><td>activation of lipolysis and lipid oxidation</td><td>intensification proteolysis</td><td>hydropenias organism in step 1, in step II hyperhydration</td></tr>
<tr><td colspan="6">Substrate and increased oxygen supply function of organs and their systems</td></tr>
</table>

Exchange fats

Exchange of fat at a fever is characterized by a predominance of catabolic processes, especially when prolonged stage II. This is evidenced by reduction in the respiratory rate to 0.5-0.7. Given the increased consumption of carbohydrates and anticipating their growing shortage in the body, oxidation of lipids is disabled at stages of intermediates, mostly - CT. In addition to metabolic disorders, this leads to an increase of acidosis. In this regard, during prolonged fevers, patients need to consume large amounts of carbohydrates.

Protein metabolism

Protein metabolism in acute moderate fever usually does not significantly upset. Proteolysis significantly increased, as evidenced by a negative nitrogen metabolism. Chronic febrile reaction, especially when a significant increase in body temperature can lead to a breach of plastic processes, the development of dystrophy in various organs and aggravate disorders life of the organism as a whole.

Water metabolism

Water exchange is subject to significant changes.

6. Phase I increased body fluid loss due to sweating and diuresis.
7. In step II feverish reaction activated release of adrenal corticosteroids (including aldosterone) and ADH in the pituitary. These hormones activate the reabsorption of water in the renal tubules, and therefore the amount of it in the body increases.
8. In Phase III ADH and aldosterone content is reduced, thanks to the excretion of fluids from the body (diuresis) increases.

Electrolytes

Exchange electrolytes at fever developing dynamically changed.

7. At stages I and II accumulate in many tissues Na +, Ca2 +, and certain other C1 ions.
8. In Phase III ions excreted in large quantities due to increased diuresis and sweating.

Other types of metabolism

Other types of metabolism in rush current classical usually not significantly altered. However, if the fever is accompanied by disruption of the structure or function of any of the bodies and their systems, then there are their characteristic changes (eg, kidney, liver or heart failure, various endocrinopathies, malabsorption syndromes). When the fever of infectious origin join their characteristic disorders (such as cholera, typhoid fever, malaria).

Functions of organs and physiological systems in fever When fever vary the function of organs and physiological systems. Causes:

- Effects on the primary pyrogenic agent of an infectious or non-infectious origin,
- Vibrations (often significant) in body temperature,
- The impact of the regulatory systems of the body,
- Involvement of authorities in the implementation of various thermoregulatory responses.

Therefore, a particular deviation of organ functions in a feverish reaction is their reaction to the integrative factors mentioned above; Biology is the "meaning" of such changes - to ensure optimal functioning of the body in these conditions. However, fever is often damaged and the authorities themselves.

Nervous system

Most infectious and non-pyrogenic, leukocyte and pyrogenic cytokines do not have a damaging effect on specific neural structures. They cause a metabolic and / or functional responses. The reasons for changes in the structure, function and metabolism of the nervous system in the course of fever include fever effect of etiological factors and secondary disorders in the body.

Manifestations

6. Non-specific neuro-psychiatric disorders: irritability, poor sleep, drowsiness, headache, confusion, lethargy, and sometimes - hallucinations.
7. Increased sensitivity of the skin and mucous membranes.
8. Violation of reflexes.
9. Changes in sensitivity to pain, neuropathy.

Endocrine system

The system of endocrine glands is involved in most of the processes developing in the body for fever as a component of a complex organism to adapt the system to the action of the pyrogenic factor and as an object of various pathogenic influences on it.

Manifestations

5. The activation of the hypothalamic-pituitary complex leads to an increase in the synthesis of certain liberinov and ADH in the hypothalamus.
6. Increased production of ACTH and TSH in the adenohypophysis.
7. Increase in blood levels of corticosteroids, catecholamines, T3 and T4, insulin.
8. Changing the content of the so-called tissue, local BAS - Pg, leukotrienes, kinins, and others.

The cardiovascular system

Reasons for change in the CVS functions: stages fluctuations neuroendocrine effects on her body and the temperature deviation.

Manifestations

6. Tachycardia, often - arrhythmia.
7. Hypertensive reaction.
8. Centralization of blood flow.

In I and Phase II of the initial stage is dominated by the effects of fever sympathetic-adrenal, hypothalamic-pituitary-adrenal and thyroid systems. With the development and completion of Phase II, these changes or offset (in uncomplicated fever during) or worse (with complications). In step III fever deviation CVS activity usually gradually eliminated. The exception is the situation, combined with a critical drop in temperature when the possible development of severe disorders of cardiac and vascular tone: arrhythmias (including fatal), heart failure, hypo- or hypertensive reactions, collapse, fainting and others.

External respiration

The volume of alveolar ventilation for the development of fever varies considerably. Causes fluctuations in intensity and changes in metabolism character deviation of blood pressure and blood oxygenation disorders and as a consequence - the pH level shifts and pC02.

Manifestations

Typically, an increase in body temperature is increasing the volume of lung ventilation. The frequency and depth of breathing changed in different ways: unidirectionally or in different directions (for example, increasing the depth of breathing may be associated with a reduction in their frequency, and vice versa). The main respiratory stimulants are pC02 increase and decrease in the pH of the blood. Activation of gas exchange in the lungs helps to increase perfusion of blood during the development of the phenomenon of centralization of blood flow.

Digestive system

The digestive system is not directly involved in the implementation of the mechanisms of fever. To a greater extent the digestive system - the object of influence of pathogenic factors feverish reaction.

Manifestations

- Loss of appetite.
- Reduction of salivation, secretory, motor and digestive functions of the stomach and intestines (to a large extent as a result of the activation of the sympathetic-adrenal system, intoxication, increased body temperature and other influences).
- Inhibition of the formation of digestive enzymes by the pancreas and bile by the liver. As a result, develop: malabsorption and digestion of food components, bloating, constipation, and sometimes nausea and vomiting.

Kidney function

Febrile reaction, usually not directly cause disorders of kidney function. Identify changes reflect a restructuring of the different regulatory mechanisms and functions of other organs and systems in fever. Thus, an increase in urine output to I and at the initial stage of stage II fever is the result of the activation of the sympathetic-adrenal effects and increasing the filtration pressure.

water accumulation in tissues with the subsequent development of fever (in particular, as a result of increased incretion of aldosterone), accompanied by a decrease in urine output.

The functions of other organs and systems in fever is not usually violated. These changes are mainly adaptive directionality.

Significance fever

Fever - a common thermoregulatory response of the body to the effects of pyrogenic agents. This typical, stereotypical reaction in each individual patient is accompanied by both adaptive (mostly), and, under certain conditions, pathogenic (less) effects.

Adaptive effects fever

The leading criterion for assessing the value of fever is a criterion to achieve the body of useful adaptive result. It is the development of such a reaction that provides the inactivation and / or destruction of the pyrogenic properties of the carrier and usually (although not always) - increased resistance to this organism as well as to other similar effects.

By the adaptive effects of fever include direct and indirect bacteriostatic and bactericidal effects, potentiation of specific and nonspecific factors NBI system, the activation of nonspecific stress reaction.

Bacteriostatic and bactericidal effects

Bacteriostatic and bactericidal effects are achieved by dividing the inhibition of many microorganisms and waste at a temperature in the range of 39-40 ° C.

Potentiation factors immunobiological systems

Improving the efficiency of a nonspecific (lysozyme, complement factor, interferon, phagocytosis, cationic proteins, etc.), And specific (synthesis of Ig, generation of T-lymphocytes and their activation, etc.). IBN mechanisms provides for detection, inactivation / degradation and elimination of foreign agents of infectious and non-infectious origin.

Activation of the stress response

Changes in the body during stress, developing on the one hand, activate and / or potentiate a number of specific and nonspecific reactions NBI system, and on the other - Plastic facilitate changing processes and functions of the physiological systems involved in the formation of febrile reactions.

Pathogenic significance of fever

The main pathogenic effects of fever			
The damaging effect of excessive heat	Pathogenic action causes fever	Functional overload of organs and systems, participating in the development of fever	disorder of functions of organs and systems that are not directly involved in the development of fever

The disorder the body's vital functions Fever is biologically negative - pathogenic significance.

Reasons fever (e.g., microbial endo- and exotoxins, foreign proteins and other compounds) may cause immunopathological processes (allergies, immunodeficiencies, autoaggression immune disease), as well as biologically non-useful reaction (arterial hyper- or hypotension, change of sensitivity to neurotransmitters and hormones , increased permeability of the vessel walls, and others.).

4) Direct and indirect damaging effect of high temperature.

5) Functional overload organs and physiological systems include direct mechanism of fever, can lead to pathological reactions. So, with a significant increase in body temperature, as well as its critical fall can develop collapse, fainting or heart failure; in infectious fever with hydropenias (eg cholera) or massive hemolysis (malaria) may disrupt hemostasis with the development of a hypercoagulable blood proteins, and even mikrotrombov DIC.

JJ. It is possible and mediated disorder of the functions of organs and systems that are not directly involved in the febrile reaction (for example, the digestive system, which is accompanied by loss of appetite, digestive disorders, malabsorption of nutrients, and the patient's weight loss, nervous system, accompanied by a headache, and sometimes convulsions and hallucinations, violation of reflexes).

DIFFERENCES FROM FEVER HYPERTHERMIC STATES AND REACTIONS Fever should be distinguished from other states and from hyperthermia hyperthermic reactions.

1. Fever

13. The cause of the fever is cake.

14. At the heart of the development of fever is a transition to a new system of thermoregulation - a higher functional level.

15. If fever persists thermoregulatory mechanisms of the organism.

These signs are used to differentiate fever from a qualitatively different state of the body overheating (hyperthermia).

- The cause of hyperthermia (overheating of the body) often is a high ambient temperature.
- A key element of the pathogenesis of overheating of the body is the failure of thermoregulation mechanisms.

From fever and hyperthermia should be distinguished hyperthermic reaction of the body. 3. Hyperthermic reactions

- The reason for hyperthermic reactions are non-pyrogenic agents.
- At the heart of hyperthermic reactions usually lies on a temporary predominance of heat emissivity.
- Mechanisms of thermoregulation of the organism are retained.
- Manifest hyperthermic response, usually moderate (within the upper limit of normal, or slightly above it) fever. The exception is malignant hyperthermia.
- On the criterion of origin distinguish hyperthermic reaction of endogenous (psychogenic, neurogenic, endocrine, due to genetic predisposition), exogenous (drug and non-drug) and combined (eg, malignant hyperthermia).

Endogenous hyperthermia reaction

Endogenous hyperthermic reactions are divided into psychogenic, neurogenic and endocrine.

1. Psychogenic hyperthermic reactions

Reasons for psychogenic hyperthermic reactions:

- Significant emotional stress (for example, students in the exam, from lecturers and actors in the solution of vital problems when exposed to stress factors).
- Some mental disorders (eg, hysteria).
- Neurotic state.

The main mechanism of psychogenic hyperthermic reactions: a significant activation of the sympathetic-adrenal and thyroid systems.

2. Neurogenic hyperthermic reactions

Neurogenic hyperthermic reactions are divided into centrogenic and reflex.

2. Centrogenic hyperthermic reactions occur during stimulation of the thermoregulatory center neurons (mainly - heat production), as well as the associated cortex and brainstem areas involved in the process of regulation of the heat balance of the body. Causes local hemorrhage, trauma, tumor, aneurysm in the above areas of the brain. Leading the development of mechanisms: the activation of the hypothalamic neurons certain zones (heat production centers of the sympathetic nervous system, synthesizing thyroliberin neurosecretory cells), as well as pituitary adenocytes synthesizing TSH. Can not be excluded that an increase in body temperature during hyperthermia neurogenic partly a result of the formation of endogenous pyrogens (in case of damage and destruction of the tissues of the body) with the connection mechanism of thermogenesis, peculiar fever.

- Reflex hyperthermic reactions occur when a strong stimulation (usually pain) in various organs and tissues of the body: the liver bile passages and biliary tract; pelvis of the kidneys and urinary tract when passing them stones; various organs during gastroscopy, colonoscopy, laparoscopy, cystoscopy. The main reason: irritation of the reflex zones, causing a strong activation of the sympathetic-adrenal and thyroid systems. The main mechanism: the intensification of metabolic reactions, combined with an increased formation of heat in the body.

3. Endocrine hyperthermic reactions

Endocrine Causes hyperthermic reactions hyperproduction of catecholamines (such as in pheochromocytoma) and / or thyroid hormones (in various forms hyperthyroid states).

Drive mechanism: exothermic activation of metabolic processes, including the formation of oxidation and phosphorylation releasers.

Exogenous hyperthermic reactions

Exogenous hyperthermic reactions are divided into drug and non-drug.

1. Medicinal hyperthermic reactions

Causes of drug (medicinal, pharmacological) hyperthermic reactions: drugs of different groups that have, in addition to the main effect, and also a thermogenic effect. examples:

- Sympathomimetics (such as catecholamine drugs, caffeine, ephedrine, L-dopa, and others.).
- Preparations containing thyroid hormones (e.g., T4) or progesterone.
- Tools that have the properties uncouple the processes of oxidation and phosphorylation (eg, containing Ca2 +, IVH, oligomycin).

2. Non-drug hyperthermic reactions

Nondrugs hyperthermic response can cause substances with thermogenic properties. Examples of such substances can be 2,4-dinitrophenol, cyanide, amytal. As a rule, they are used for research purposes (eg, in experiments on animals), ingested accidentally or as a result of violation of safety in their production.

The mechanism of development - stimulate the thermogenic processes in the body:

- Activation of the sympathetic-adrenal and thyroid systems;
- Stimulation of adrenergic receptors, thyroid hormone receptors;
- Uncoupling of oxidation and phosphorylation.

PRINCIPLES AND METHODS FOR THE TREATMENT OF FEVER

Fever Treatment constructed taking into account the requirements etiotrop, pathogenetic and symptomatic principles. However, it must be remembered that the increase in body temperature during fever has adaptive value, consisting in the activation of protective, adaptive and compensatory reactions aimed at the destruction or weakening of pathogenic agents. Among these reactions are cellular and humoral immunity, nonspecific protection factors (phagocytosis, lysozyme, complement factors), cytokines, metabolic reactions, plastic processes.

Etiotropic treatment

Etiotropic treatment is aimed at eliminating and / or termination of the pyrogenic agent.

6. When an infectious fever of antimicrobial treatment. At the same antibiotics, sulfa drugs, antiseptics and other means are used, taking into account the sensitivity of pathogens to them.
7. When taking measures for fever infectious origin:

5. Cessation of contact (or administration) to a pyrogen (whole blood or plasma, vaccines, sera, protein-containing substances and the like);
6. Removal from the body source of pyrogenic agents (eg, necrotic tissue, the contents of the abscess, tumor).

3. Regardless of the origin of the primary pie, possible to carry out activities for the inhibition of the synthesis and effects of action of leukocyte pyrogens (IL-1, IL-6, Name, y-IFN and others.).

Pathogenetic therapy

Pathogenetic therapy aims at blockade of the key elements of the pathogenesis and as a consequence - reducing the excessively high body temperature. This is achieved by:

4. Braking products, prevent or reduce the effects of the substances produced in the neurons of thermoregulatory center under the influence of leukocyte cytokines PGE, cAMP, leading to the activation of heat mechanisms. Widely used for this synthesis blockers Pg - acetylsalicylic acid (aspirin) and other NSAIDs or pyrazole derivative - aminopyrine.
5. Reduction of excessive heat production by suppressing the intensity of oxidation reactions. The latter can be achieved, for example, by the use of quinine drugs.

Carrying antipyretic therapy is necessary only when there is or perhaps a damaging effect on the body's vital functions of hyperthermia:

6. Excessive (hyperpyretic) increase in body temperature.
7. Patients with decompensated diabetes or circulatory failure.
8. In neonates, infants and the elderly with an imperfect system of thermoregulation of the body.

When the fever of infectious origin holding antipyretic therapy requires weighty justification, as it is shown that antipyretic agents reduce the efficiency of phagocytosis, immune reactions, increase the duration of infectious processes, the incidence of complications.

Symptomatic treatment

Symptomatic treatment aims to eliminate the problem of painful and unpleasant sensations and conditions exacerbate the patient's status. When a fever These symptoms include severe headache, nausea and vomiting, pain in joints and muscles ("breaking"), cardiac arrhythmia. With these and other such attributes apply appropriate medications and non-drug products (pain relievers, tranquilizers, cardiotropic et al.).

Pyrotherapy

Artificial hyperthermia (pyrotherapy) used in medicine since ancient times. Currently pyrotherapy curative is used in combination with other non-drug and drug effects nature. There are general and local pyrotherapy.

Total pyrotherapy

The total spend by playing pyrotherapy fever using purified pyrogen (eg pyrogenal or substances that stimulate the synthesis of endogenous pyrogens). A moderate increase in body temperature during fever stimulates adaptive processes in the body:

5. Specific and nonspecific mechanisms IBN system (under certain infectious processes - syphilis, gonorrhea, postinfectious arthritis);
6. Plastic and reparative processes in the bones, tissues and parenchymal organs (for their destruction, damage, dystrophy, after surgery).

Local hyperthermia

Local hyperthermia per se, as well as in combination with other treatments to reproduce the stimulation of regional protection mechanisms (immune and non-immune), repair and circulation. Regional hyperthermia induced by chronic inflammation, erosions and ulcers of the skin, subcutaneous tissue, as well as certain forms of cancer.

In oncology, hyperthermia is used in connection with several of its possible anticancer effects.

- Inhibition of mitosis (especially in S-phase) in tumor cells. It is shown experimentally that the increase in temperature carcinoma cells from 43 to 44 ° C reduces their survival 1.5-2.
- Denaturation of membrane proteins, LP and many enzymes neoplastic cells, combined with their overhydration and destruction.
- The increase in tissue glutathione tumor damaging the DNA of tumor cells.
- Increased blood viscosity and a violation of microcirculation in the vessels of the tumor, the growth in its hypoxia, acidosis, hyperosmia reducing the viability of cancer cells.
- Potentiation of the effects of chemo-, radio- and immunotherapy.

NEOPLASIA

Neoplasm is an abnormal mass of tissue as a result of **neoplasia**. Neoplasia (*new growth* in Greek) is the abnormal proliferation of cells, it is a widespread and potentially grave growth abnormality (dystrophic proliferation). The growth of this clone of cells exceeds, and is uncoordinated with, that of the normal tissues around it. It usually causes a lump or **tumor**.

Cancer is a disease of growth, division and cell differentiation, it is the result of mutation of genes controlling these processes (protooncogenes and cancer suppressor genes).

Cancer is synonymous with malignant tumor; the Latin cancer is actually a literal translation of the Greek karkinos for crab, a common creature on Mediterranean shores. In the Hippocratic books, karkinos and karkinoma are used for conditions that we would almost certainly call carcinoma (epithelial cancer) or, more generally, cancer. There seem to have been many reasons for borrowing

the image of the crab, and the choice was extraordinarily successful: the name of the innocent crustacean has become a sinister metaphor, even for the destructive ills of society

Tumor is a typical pathologic process characterized by irregulated limitless growth of the tissue, which is not connected with the general structure of the impaired organ and its functions.

Tumor is growing from itself, i.e. it grows as a result of reproduction of even one malignant cell. The tissue of tumors differs from the original one by structure, physical and chemical, biochemical, functional and other signs. It is called *atypism.* These changes indicate anaplasia that is returning of the cell to its embryonic state and also metaplasia — acquisition of properties of other tissue.

Table. Epidemiology of human cancer

Male		Female	
most common (by occurrence)	most common (by mortality)	most common (by occurrence)	most common (by mortality)
prostate cancer (25%)	lung cancer (31%)	breast cancer (26%)	lung cancer (26%)
lung cancer (15%)	prostate cancer (10%)	lung cancer (14%)	breast cancer (15%)
colorectal cancer (10%)	colorectal cancer (8%)	colorectal cancer (10%)	colorectal cancer (9%)
bladder cancer (7%)	pancreatic cancer (6%)	endometrial cancer (7%)	pancreatic cancer (6%)
non-Hodgkin lymphoma (5%)	liver & intrahepatic bile duct (4%)	non-Hodgkin lymphoma (4%)	ovarian cancer (6%)

Cancer is a global problem, and with reference to the globe, it is also a spotty problem. By definition, the task of epidemiology is to explain why a particular patient developed a particular disease at a particular time and place. Its ultimate goal is to find all causes of all diseases and to suggest preventive measures for every one.

The two basic rules of cancer epidemiology are that all types of cancer can occur everywhere, and that the incidence of each type varies from place to place. The lowest incidence of a particular cancer observed anywhere on the globe is taken to represent the baseline for that cancer, which is due to shared genetic and/or environmental factors. Any higher incidence is interpreted as reflecting some special local cause, usually environmental. This rule has been exploited for detecting causes in high-incidence populations.

We should recall here that incidence is the number of new cases in a population during a given period. Prevalence is the number of existing cases at a given time.

1. Types of tumors

When discussing human tumors, we will use the traditional distinction between benign tumors (slowly growing, noninfiltrating, not fatal) and malignant tumors (more rapidly growing, infiltrating, metastasizing, and if untreated fatal). When discussing experimental carcinogenesis, we will follow the party line of the experts: tumors are malignant or on the way to malignancy.

A benign tumor is a tumor that lacks all three of the malignant properties of a cancer. Thus, by definition, a benign tumor does not grow in an unlimited, aggressive manner, does not invade surrounding tissues, and does not metastasize. Common examples of benign tumors include moles and uterine fibroids.

The term "benign" implies a mild and nonprogressive disease, and indeed, many kinds of benign tumor are harmless to the health. However, some neoplasms which are defined as 'benign tumors' because they lack the invasive properties of a cancer, may still produce negative health effects. Examples of this include tumors which produce a "mass effect" (compression of vital organs such as

blood vessels), or "functional" tumors of endocrine tissues, which may overproduce certain hormones (examples include thyroid adenomas, adrenocortical adenomas, and pituitary adenomas).

Benign tumors typically are encapsulated, which inhibits their ability to behave in a malignant manner. Nonetheless, many types of benign tumors have the potential to become malignant and some types, such as teratoma, are notorious for this.

Malignant neoplasm or malignant tumor: synonymous with cancer.

Table. Summary of features differentiating benign and malignant neoplasms.

Feature	In Benign Tumors	In Malignant Tumors
Rate of growth	Slow	Fast
Mode of growth	Expansile	Infiltrative
General effects	Uncommon (except endocrine)	Common
Metastases	No	Common
Recurrence after removal	Rare	Common
Gross:		
Capsule	Common	Pseudocapsule
Necrosis	Rare	Common
Ulceration	Rare	Common
Microscopic:		
Atypia	Mild	Severe
Pleomorphism	Mild	Severe
Mitoses	Few	Many
Nuclear/cytoplasmic ratio	Normal	Increased
Nucleolus	Normal	Prominent
Ploidy	Often normal	Usually abnormal

2. Grading and staging of cancer

Methods to quantify the probable clinical aggressiveness of a given neoplasm and to express its apparent extent and spread in the individual patient are necessary for comparisons of end results of various forms of treatment. The **grading** of a cancer attempts to establish some estimate of its aggressiveness or level of malignancy based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor. The cancer may be classified as grade I, II, III, or IV, in order of increasing anaplasia.

Staging of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of metastases. Two methods of staging are currently in use: the TNM system (*T*, primary tumor; *N*, regional lymph node involvement; *M*, metastases). In the TNM system, T1, T2, T3, and T4 describe the increasing size of the primary lesion; N0, N1, N2, and N3 indicate progressively advancing node involvement; and M0 and M1 reflect the absence or presence of distant metastases.

3. Etiology and pathogenesis

Risk factors

Some mistakes in DNA replication throughout a lifetime are inevitable. However, certain conditions or behaviors, known as risk factors, can increase or decrease the likelihood of a mutation arising and a mutated cell being promoted until it is cancerous.

Geographic variations in the overall incidence of cancer and in the incidence of specific types of cancer also occur from one country to another, from one city to another, and from urban to rural areas. Detailed epidemiologic case control studies have sometimes uncovered associations with high-risk occupations, diet, environmental carcinogens, or endemic viruses; other occurrences remain unexplained. For example, the high incidence of stomach cancer in Japan has been related to diet

(smoked raw fish). This type of cancer does not appear to be genetically determined, because Japanese emigrating to the United States show within a single generation the lower incidence of stomach cancer demonstrated by native-born Americans.

Behavioral risk factors. Certain behaviors increase the likelihood that an individual will be frequently exposed to cancer-causing stimuli. Behavioral risk factors include cigarette smoking and diets rich in animal fat and preserved meats. Approximately a third of all cancers can be attributed to cigarette smoking, and a third to diet. Obesity also may be an independent risk factor for cancer because of the increased accumulation of fat-soluble toxins and potentially carcinogenic hormones in fatty tissue. Even a low level of alcohol consumption is linked to an increase in breast cancer, as is a sedentary lifestyle. Other behavioral risk factors include those associated with sexual behavior. A high number of sexual partners and an early onset of sexual activity increase the risk of becoming infected with the human papilloma virus (HPV), which is associated with genital neoplasms, and the AIDS virus, which is associated with Kaposi's sarcoma.

Hormonal Risk Factors. Estrogen may act as a promoter for certain cancers, such as breast and endometrial cancer. Because estrogen levels are high in menstruating women, the risk for developing breast cancer is increased in women who started menstruating early and reached menopause late. Delayed childbearing or choosing not to bear children increases the risk of breast cancer. Estrogen replacement therapy in postmenopausal women appears to be associated with an increase in the risk of breast cancer.

Inherited Risk Factors. A family history of cancer, especially clustered as one type, is a risk factor for developing cancer. Genetic tendencies for carcinogenesis may involve fragile or mutated tumor suppressor genes, susceptibility to certain mutagens or promoters, faulty proofreading enzymes, or a poorly functioning immune system. Inherited defects in the p53 gene have been documented to be associated with a high risk of cancer. Certain cancers have a higher tendency to run in families than others. For example, although most cases of colon cancer arise spontaneously, some families carry mutations that increase the risk of this disease.

Pediatric cancers likely have a genetic component. In children, the development of cancer is accelerated from several decades to only one or two decades. Acceleration may occur if a child inherits in the germ line (egg or sperm) one defective gene controlling a tumor suppressor or proto-oncogene product or develops such a mutation early in embryogenesis. Later, a second gene error would cause early cancer growth. Similarly, inheriting defective genes for proofreading enzymes would increase the risk of early cancer development.

History of Associated Diseases. Perhaps the most important finding in the history of a patient with suspected cancer is a record of diagnosis or treatment of previous cancer which greatly increases the chances that the current illness represents either a metastasis or a second primary tumor. Statistics show that patients who have had cancer—have a much higher incidence of a second cancer, particularly in the same tissue. For example, cancer in one breast increases the chances of cancer in the opposite breast. Second cancers of a different type—particularly leukemia and sarcomas—also occur as a complication of chemotherapy and radiation used to treat the first cancer.

In addition, certain disorders that in themselves are nonneoplastic carry an associated higher risk of development of cancer and are considered **preneoplastic diseases.** These diseases are uncommon, but together they constitute a significant group of risk factors.

Table. The preneoplastic diseases

Nonneoplastic or preneoplastic condition	**Neoplasm**

Down Syndrome (trisomy 21)	Acute myeloid leukemia
Xeroderma pigmentosum (plus sun exposure)-	Squamous cancer of skin
Gastric atrophy (pernicious anemia)-	Gastric cancer

Factors that are protective against cancer development

Studies suggest that women who breastfeed for at least 6 consecutive months have a reduced risk of developing breast cancer. In addition, women who have had multiple pregnancies have a reduced risk of breast cancer. Progesterone is high during pregnancy and appears to be protective against breast cancer by inhibiting the stimulatory effects of estrogen.

Dietary factors are important in reducing cancer risk. Diets rich in substances known to scavenge or remove dangerous free radicals, called free-radical scavengers or antioxidants, may reduce the risk of certain cancers. These substances include vitamins A, E, and C and folic acid, all of which are prevalent in green, leafy and colorful vegetables and fruits.

Mechanisms of gene activation & inactivation

Cancer is a diverse class of diseases which differ widely in their causes and biology. Any organism, even plants, can acquire cancer. Nearly all known cancers arise gradually, as errors build up in the cancer cell and its progeny.

Anything which replicates (our cells) will probabilistically suffer from errors (mutations). Unless error correction and prevention is properly carried out, the errors will survive, and might be passed along to daughter cells. Normally, the body safeguards against cancer via numerous methods, such as: apoptosis, helper molecules (some DNA polymerases), possibly senescence, etc. However these error-correction methods often fail in small ways, especially in environments that make errors more likely to arise and propagate. For example, such environments can include the presence of disruptive substances called carcinogens, or periodic injury (physical, heat, etc.), or environments that cells did not evolve to withstand, such as hypoxia (see subsections). Cancer is thus a progressive disease, and these progressive errors slowly accumulate until a cell begins to act contrary to its function in the animal.

It has been suggested that neoplastic transformation occurs as a result of activation (or derepression) of growth promoter genes (proto-oncogenes) or inactivation or loss of suppressor genes. **Activation** is a functional concept whereby the normal action of growth regulation is diverted into oncogenesis. The resultant activated proto-oncogene is referred to as an **activated oncogene** (or a mutant oncogene, if structurally changed), or simply as a **cellular oncogene (c-*onc*).** Activation and inactivation may occur through several mechanisms: (1) **mutation,** including single nucleotide loss (frameshift) or substitution (nonsense or missense codon), codon loss, gene deletion or more major chromosomal loss; (2) **translocation** to a different part of the genome where regulatory influences may favor inappropriate expression or repression; (3) **insertion of an oncogenic virus** at an adjacent site; (4) **amplification** (production of multiple copies of the proto-oncogenes), which appear as additional chromosome bands or extra DNA fragments (double minutes); (5) **introduction of viral oncogenes**; or (6) **derepression** (loss of suppressor control).

Carcinogens

An agent that causes neoplasms is an oncogenic agent; an agent causing a malignant neoplasm (cancer) is a carcinogenic agent. Carcinogens are substances that are known to cause cancer or at least produce an increased incidence of cancer in an animal or human population. Many carcinogens have been identified in experimental animals, but because of dose-related effects and
the metabolic differences among species, the relevance of these studies to humans is not always clear. It is important to stress that (1) the cause of most common human cancers is unknown; (2) most cases of cancer are probably multifactorial in origin; and (3) except for cigarette smoking, the agents discussed below have been implicated in only a small percentage of cases.

4. Chemical carcinogenesis

It has been over 200 years since the London surgeon Sir Percival Pott correctly attributed scrotal skin cancer in chimney sweeps to chronic exposure to soot. A few years later, based on this observation, the Danish Chimney Sweeps Guild ruled that its members must bathe daily. No public health measure since that time has achieved so much in the control of a form of cancer. Since that time, hundreds of chemicals have been shown to be carcinogenic in animals.

Main characteristic of chemicals carcinogens.

6. They are of extremely diverse structure and include natural and synthetic products.

7. Some are direct reacting and require no chemical transformation to induce carcinogenicity, but most are indirect reacting and become active only after metabolic conversion. Such agents are referred to as *procarcinogens*, and their active end products are called *ultimate carcinogens*.

8. All direct-reacting and ultimate chemical carcinogens are highly reactive electrophiles (i.e., have electron-deficient atoms) that react with the electron-rich atoms in RNA, cellular proteins, and, mainly, DNA.

9. The carcinogenicity of some chemicals is augmented by agents that by themselves have little, if any, transforming activity. Such augmenting agents traditionally have been called *promoters*; however, many carcinogens have no requirement for promoting agents.

10. Several chemical carcinogens may act in concert with other types of carcinogenic influences (e.g., viruses or radiation) to induce neoplasia.

Direct-acting agents, as already noted, require no metabolic conversion to become carcinogenic. They are in general weak carcinogens but are important because some of them are cancer chemotherapeutic drugs (e.g., alkylating agents) that have successfully cured, controlled, or delayed recurrence of certain types of cancer (e.g., leukemia, lymphoma). This situation is even more tragic when their initial use has been for non-neoplastic disorders, such as rheumatoid arthritis. The risk of induced cancer is low, but the fact that it exists dictates judicious use of such agents.

The designation *indirect-acting agent* refers to chemicals that require metabolic conversion before they become active. Some of the most potent indirect chemical carcinogens-the polycyclic hydrocarbons-are present in fossil fuels. Polycyclic agents may be produced in the combustion of organic substances. For example, benzo[*a*]pyrene and other carcinogens are formed in the high-temperature combustion of tobacco in cigarette smoking. *These products are implicated in the causation of lung cancer in cigarette smokers*.

Polycyclic hydrocarbons also may be produced from animal fats during the process of broiling meats and are present in smoked meats and fish. The principal active products in many hydrocarbons are epoxides, which form covalent adducts (addition products) with molecules in the cell, principally DNA, but also with RNA and proteins. Aflatoxin B_1 is of interest because it is a naturally occurring agent produced by some strains of *Aspergillus*, a mold that grows on improperly stored grains and nuts. There is a strong correlation between the dietary level of this food contaminant and the incidence of hepatocellular carcinoma in some parts of Africa and the Far East.

Saccharin and cyclamates have been incriminated as carcinogens in experimental animals, but because induction of cancer with these artificial sweeteners requires extremely large doses, their role in human carcinogenesis remains in doubt. Finally, vinyl chloride, arsenic, nickel, chromium, insecticides, fungicides, and polychlorinated biphenyls (PCBs) are potential carcinogens in the workplace and about the house.

Mechanisms of action of chemical carcinogens

cause malignant transformation results from mutations that affect protooncogenes and cancer suppressor genes, it should come as no surprise that most chemical carcinogens are mutagenic. Although any gene may be the target of chemical carcinogens, *RAS* gene mutations are particularly common in several chemically induced cancers in rodents. Among tumor suppressor genes, *TP53* is an important target. Specific chemical carcinogens, such as aflatoxin B_1, produce characteristic mutations in the *TP53* gene. The association is sufficiently strong to incriminate aflatoxin, if the

analysis of the *TP53* gene reveals the *signature* mutation. These associations are proving useful tools in epidemiologic studies of chemical carcinogenesis.

It was mentioned earlier that carcinogenicity of some chemicals is augmented by subsequent administration of ***promoters*** (e.g., phorbol esters, hormones, phenols, and drugs) that by themselves are nontumorigenic. To be effective, repeated or sustained exposure to the promoter must *follow* the application of the mutagenic chemical, or ***initiator***. The initiation-promotion sequence of chemical carcinogenesis raises an important question: Since promoters are not mutagenic, how do they contribute to tumorigenesis? Although the effects of tumor promoters are pleiotropic, *induction of cell proliferation is a sine qua non of tumor promotion*. Tetra-decanoylphorbol-acetate (TPA), a phorbol ester and the best-studied tumor promoter, is a powerful activator of protein kinase C, an enzyme that is a crucial component of several signal transduction pathways, including those activated by growth factors. TPA also causes growth factor secretion by some cells. It seems most likely that while the application of an initiator may cause the mutational activation of an oncogene such as *RAS*, subsequent application of promoters leads to clonal expansion of initiated (mutated) cells. Such cells (especially after *RAS* activation) have reduced growth factor requirements and may be less responsive to growth-inhibitory signals in their extracellular milieu. Forced to proliferate, the initiated clone of cells suffers additional mutations, developing eventually into a malignant tumor.

The concept that sustained cell proliferation increases the risk of mutagenesis, and hence neoplastic transformation, is also applicable to human carcinogenesis. The influence of estrogens on the occurrence of breast cancers may relate in part to the proliferative effects of estrogen on mammary ductal epithelium. The fact that many breast cancers express estrogen receptors and benefit from estrogen receptor antagonists supports a role for estrogen in breast cancer.

It must be emphasized that carcinogen-induced damage to DNA does not necessarily lead to initiation of cancer. Several forms of DNA damage (incurred spontaneously or through the action of carcinogens) can be repaired by cellular enzymes. Were this not the case, the incidence of environmentally induced cancer in all likelihood would be much higher.

5. Physical carcinogenesis

In group of physical factors of tumorogenesis the most important and most often is radiation, whatever its source-UV rays of sunlight, x-rays, nuclear fission, radionuclides is an established carcinogen. The evidence is so voluminous that only a few examples are given. Many of the pioneers in the development of roentgen rays developed skin cancers. Miners of radioactive elements have suffered a ten-fold increased incidence of lung cancers. Follow-up of survivors of the atomic bombs dropped on Hiroshima and Nagasaki disclosed a markedly increased incidence of leukemia-principally acute and chronic myelocytic leukemia-after an average latent period of about 7 years. Decades later, the leukemia risk for individuals heavily exposed is still above the level for control populations, as is the mortality rate from thyroid, breast, colon, and pulmonary carcinomas and others. The nuclear power accident at Chernobyl in the former Soviet Union continues to exact its toll in the form of high cancer incidence in the surrounding areas. Even therapeutic irradiation has been documented to be carcinogenic. Papillary thyroid cancers have developed in approximately 9% of individuals exposed during infancy and childhood to head and neck irradiation.

It is abundantly clear that radiation is strongly oncogenic. This effect of ionizing radiation is related to its mutagenic effects; it causes chromosome breakage, translocations, and, less frequently, point mutations. This effects may be due to activation of lipid peroxidation. Biologically, double-

stranded DNA breaks seem to be the most important for radiation carcinogenesis. There also is some evidence that nonlethal doses of radiation may induce genomic instability, favoring carcinogenesis. Because the latent period of irradiation-associated cancers is extremely long, it seems that cancers emerge only after the progeny of initially damaged cells accumulate additional mutations, induced possibly by other environmental factors.

The oncogenic effect of UV rays merits special mention because it highlights the importance of DNA repair in carcinogenesis. Natural UV radiation derived from the sun can cause skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas). At greatest risk are fair-skinned people who live in locales that receive a great deal of sunlight. Cancers of the exposed skin are particularly common in Australia and New Zealand. Nonmelanoma skin cancers are associated with total cumulative exposure to UV radiation, whereas melanomas are associated with intense intermittent exposure-as occurs with sunbathing. UV light has several biologic effects on cells. Of particular relevance to carcinogenesis is the ability to damage DNA by forming pyrimidine dimers. This type of DNA damage is repaired by a complex set of proteins that effect nucleotide excision repair. With extensive exposure to UV light, the repair systems may be overwhelmed, and skin cancer results. The importance of nucleotide excision repair is illustrated dramatically in an inherited disease called *xeroderma pigmentosum*. In these individuals, *the nucleotide excision repair mechanism is defective or deficient*, and there is a greatly increased predisposition to skin cancers. UV light characteristically causes mutations in the *TP53* gene. Three other disorders of DNA repair and genomic instability-ataxia-telangiectasia, Fanconi anemia, and Bloom syndrome-also are characterized by an increased risk of cancer, related to some inability to repair environmentally induced DNA damage.

6. Biological oncogenesis

The study of oncogenic retroviruses in animals has provided spectacular insights into the genetic basis of cancer. Animal retroviruses transform cells by two mechanisms. Some, called *acute transforming viruses*, contain a transforming viral oncogene *(v-onc)*, such as *V-SRC*, *V-ABL*, or *V-MYB*. Others, called *slow transforming viruses* (e.g., mouse mammary tumor virus), do not contain a v-*onc*, but the proviral DNA is always found inserted near a cellular oncogene. Under the influence of a strong retroviral promoter, the adjacent normal or mutated cellular oncogene is overexpressed. This mechanism of transformation is called *insertional mutagenesis*. With this brief summary of retroviral oncogenesis in animals, we can turn to the only known human retrovirus that is associated with cancer.

RNA oncogenic viruses

Human T-Cell Leukemia Virus Type 1. Human T-cell leukemia virus-1 (or human T-cell lymphotropic virus type 1 -HTLV-1) is associated with a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin but is found sporadically elsewhere. HTLV-1 has tropism for CD41 T cells, and this subset of T cells is the major target for neoplastic transformation. Leukemia develops in only about 1% of infected individuals after a long latent period of 20 to 30 years.

HTLV-1 does not contain a v-*onc*, and in contrast to slow transforming retroviruses, no consistent integration next to a cellular oncogene has been discovered, but in addition to the usual retroviral genes, a unique region called *pX* which encodes several proteins, including one called TAX. The TAX protein can activate the transcription of several host cell genes, including genes encoding the cytokine IL-2 and its receptor and the gene for GM-CSF and repress the function of tumor suppressor genes (*TP53)*. The following scenario is emerging: HTLV-1 infection stimulates proliferation of T cells by the *TAX* gene, which turns on genes that encode IL-2 and its receptor, setting up an autocrine system for proliferation. Production of GM-CSF increased too. All this factors induce increased secretion of IL-1 (cell mitogen) and inhibition of growth-suppressive pathways. Initially the T-cell proliferation is polyclonal because the virus infects many cells. The proliferating T cells are at increased risk of secondary transforming events (mutations), which lead ultimately to the outgrowth of a monoclonal neoplastic T-cell population.

DNA oncogenic viruses

As with RNA viruses, several oncogenic DNA viruses that cause tumors in animals have been identified. Four DNA viruses-HPV (Human papillomavirus), Epstein-Barr virus (EBV) human herpesvirus 8 (HHV-8, also called Kaposi sarcoma herpesvirus), and HBV-are of special interest because they are strongly associated with human cancer.

Human Papillomavirus (HPV)

Epidemiologic studies suggest that carcinoma of the cervix is caused by a sexually transmitted agent, and HPV is strongly linked to this cancer. DNA sequences of HPV are found in 75% to 100% of invasive squamous cell cancers and their presumed precursors (i.e., severe dysplasias and carcinoma in situ). Infection with high-risk HPV types simulates the loss of tumor suppressor genes, activates cyclins, inhibits apoptosis, and combats cellular senescence. Infection with HPV itself is not sufficient for carcinogenesis. For example, when human keratinocytes are transfected with DNA from HPV31 in vitro, they are immortalized, but they do not form tumors in experimental animals. Cotransfection with a mutated *RAS* gene results in full malignant transformation. These data strongly suggest that HPV in all likelihood acts in concert with other environmental factors.

Epstein-Barr Virus (EBV)

EBV has been implicated in the pathogenesis of several human tumors: Burkitt lymphoma, post-transplant lymphoproliferative disease, primary central nervous system lymphoma in AIDS patients, nasopharyngeal carcinoma. Burkitt lymphoma is endemic in certain parts of Africa and is sporadic elsewhere. EBV exhibits strong tropism for B cells and infects many B cells, causing them to proliferate, immortalization of B cells. These cell lines express several EBV-encoded antigens.

The molecular basis of B-cell proliferations induced by EBV is complex. One of the EBV-encoded genes acts as an oncogene, it promotes B-cell proliferation by activating signaling pathways via the B-cell surface molecule CD40, prevents apoptosis by activating BCL2.

In immunologically normal individuals, EBV is a cause of episode of infectious mononucleosis. In regions of the world where Burkitt lymphoma is endemic, concomitant (endemic) malaria (or other infections) impairs immune competence, allowing sustained B-cell proliferation. In addition, the B cells do not express cell surface antigens that can be recognized by host T cells. Relieved from immunoregulation, such B cells are at increased risk of acquiring mutations, such as the t(8;14) translocation, which activates the *MYC* oncogene and is a consistent feature of this tumor. The activation of *MYC* causes further loss of growth control, and the stage is set for additional gene damage, which ultimately leads to the emergence of a monoclonal neoplasm.

Hepatitis B Virus (HBV)

The epidemiologic evidence linking chronic HBV infection with hepatocellular carcinoma is strong, but the mode of action of the virus in tumor production is not fully elucidated. The HBV genome does not encode any transforming proteins, and there is no consistent pattern of integration in liver cells. HBV DNA is integrated, however, in 90% of patients with liver cancer who are positive for hepatitis surface B antigen, and the tumors are clonal with respect to these insertions. The oncogenic effect of HBV seems to be multifactorial. First, by causing chronic liver cell injury and accompanying regeneration, HBV predisposes the cells to mutations, caused possibly by environmental agents (e.g., dietary toxins). Second, an HBV-encoded regulatory element called *HBx* disrupts normal growth of infected liver cells by transcriptional activation of several growth-controlling genes. Third, cytosolic signal transduction pathways (e.g., RAS-MAP kinase) are turned on (recall TAX proteins of HTLV-1). Whether HBx also causes inactivation of *TP53* is controversial. The role of the *HBx* gene in hepatic curcinogenesis is supported by the development of hepatocellular carcinomas in mice that are transgenic for this gene. Finally, in some patients, viral integration seems to cause secondary rearrangements of chromosomes, including multiple
deletions that may harbor unknown tumor suppressor genes. Thus, it seems that virus-induced gene damage in regenerating liver cells may set the stage for multistep carcinogenesis.

Although not a DNA virus, hepatitis C virus (HCV) also is strongly linked to hepatocellular carcinoma. In general, the mechanism of HCV-related liver cancer is similar to that described for HBV. Extensive death of liver cells with their regeneration, and disruption of growth regulation are important factors. Unlike HBV, HCV does not contain the X-protein.

Helicobacter pylori

First incriminated as a cause of peptic ulcers, *H. pylori* now has acquired the dubious distinction of being blamed for causation of gastric carcinoma and gastric lymphoma. Their pathogenesis involves initial chronic gastritis that causes lymphoid follicles to develop in the gastric mucosa. It is thought that *H. pylori* infection leads to the formation of *H. pylori*-reactive T cells, which in turn cause polyclonal B-cell proliferations. In time, a monoclonal B-cell tumor emerges in the proliferating B cells, perhaps as a result of accumulation of mutations in growth-regulatory genes. In keeping with this, early in the course of disease, eradication of *H. pylori* "cures" the lymphoma by removing antigenic stimulus for T cells.

In addition to B-cell lymphomas, *H. pylori* has now been linked strongly to the pathogenesis of gastric epithelial cancers. Here the scenario seems to be an initial development of chronic gastritis, followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer. This sequence takes decades to complete and occurs in only 3% of infected patients.

Although *H. pylori* causes three diseases (peptic ulcer, gastric lymphoma, and gastric carcinoma), these conditions do not occur often in the same patient. For unknown reasons, patients who have duodenal ulcers (not gastric ulcers) almost never develop gastric carcinoma.

7. Malignent cells features

Malignant cells have grate number of special characteristics, gived them ability to live in different condition. Some of them will discus here.

Structural Differences

Lack of differentiation means that the special features of the normal cell are imperfectly expressed: a ciliated cell will have fewer cilia, a secretory cell less secretion, and so on. This fact has given rise to the common and synonymous terms **anaplasia**, and **dedifferentiation**, both implying that the cancer cell has somehow regressed to a lesser state of differentiation. However, it seems unlikely that tumors consist of mature cells that regress. The current concept of carcinogenesis is that tumors contain undifferentiated stem cells whose progeny fail to mature. In other words, the tumor cell is born in a state of low differentiation and does not become immature by dedifferentiating itself.

Some kind of backward differentiation does indeed occur in malignant tumors as they change from bad to worse, a phenomenon known (backwardly) as tumor progression.

Fast growth. Features of fast-growing cells are easy to grasp:

- Cytoplasmic basophilia is increased, which means more RNA and thus more active protein synthesis. The electron microscope shows many free ribosomes, which correspond to the fact that the cell is busy making more of itself rather than producing proteins for export.
- Nucleoli increase in size and number (remember that RNA is synthesized within them), and the nucleolar organizer region may be abnormal.
- Glycogen content is high, as it is in embryonic cells. This abundance of glycogen correlates with the anaerobic glycolysis typical of embryonic as well as of tumor cells.

Atypical features. The features of atypia are especially important because atypia tends to parallel the degree of aggressiveness. It can hit virtually every aspect of cellular structure. For example:

- Size and shape of the cell are abnormal. Malignancy is linked to cytoskeletal disturbances, which lead to internal disarray as well as to mechanical effects on cell shape.

JJ The shape of the nucleus is irregular. This is one of the most reliable criteria of malignancy, especially when the size and shape of the nucleus vary from cell to cell: most of the

abnormal nuclei contained abnormal chromosomes, ring-shaped, dicentric, or with other defects. Thus, abnormalities in nuclear shape can be considered primarily as signs of genetic instability.

KK Mitoses are too numerous and some may be abnormal. Multiple centrosomes are often associated with the lack of a powerful tumor suppressor gene, p53; the lack of this controlling gene could allow centrosomes to replicate when they should not. By increasing the frequency of mitotic errors, the centrosomes could also confer a mutator phenotype to tumors.

LL Cell-specific organelles are distorted or lost.

MM Secretion becomes irregular, as best seen in mucussecreting cells.

Behavior in Culture

Immortality. Transformed cells can grow forever. A sadly famous lady named Henrietta Lacks died in 1951 of a cervical carcinoma; cells from her tumor, the ubiquitous HeLa cells, are still growing relentlessly in laboratories throughout the world. Note that this immortality does not compare with the immortality of bacteria: in real life, every strain of immortal malignant cells dies when it kills its host unless it is cultured like the HeLa cells. Every case of cancer is therefore a new disease. Telomere-telomerase mechanism: linear chromosomes must be capped by telomeres, which are progressively eroded (a lethal pathway for the cell) unless they are rebuilt by the enzyme telomerase. Virtually all tumors express telomerase, but telomerase expression by itself does not imply transformation, witness the telomerase-positive stem cells. Expression of the human telomere gene is regulated by the immortalizing oncoprotein Myc, which is up-regulated in most human cancers.

Loss of anchorage dependence. As mentioned earlier, normal cells prefer to grow on a surface; they become attached to it, spread out, and begin to replicate. In contrast, transformed cells can also do well in a fluid medium such as soft agar, in which they maintain a more rounded shape. Cytoskeletal changes are probably involved.

Loss of contact inhibition. Transformed cells grow to cover all available space, then continue to grow and pile up over each other haphazardly. Normal cells usually stop when they contact each other, at which point they constitute a confluent sheet with little or no cell overlap. The term contact inhibition has been used in various ways; for some it has meant inhibition of movement and for others inhibition of growth, hence the current tendency to replace the phrase loss of contact inhibition with the cumbersome decreased density-dependent inhibition of growth.

Loss of orientation on an oriented substrate. Malignant cells growing on a surface with a distinctive pattern have partially lost the ability to align themselves accordingly. This is, we presume, another consequence of a faulty cytoskeleton.

Decreased requirement for growth factors. Normal cells tend to be fussy about the medium in which they are nurtured; special mixtures of growth factors must be worked out for each type. Transformed cells are much easier to grow and require less serum (i.e., fewer growth factors). The reason is now apparent: malignant cells supply their own growth factors by a curious property known as autocrine secretion.

Functional and Biochemical Changes

Motility and chemotaxis. Many types of cancer cells can move around rather like amoebae, although their normal counterparts may be stationary. This characteristic helps us understand the mechanism of invasiveness; it was actually shown in vitro that the fastest moving cells are the most invasive. Moreover, some cancer cells secrete a factor that accelerates their motion and even directs it by chemotaxis.

Surface-related changes

- **Decreased adhesion between cells.** In a classic experiment D. R. Coman of Philadelphia showed in 1944 that cells of a carcinoma are more easily pulled apart than their normal counterparts. Malignant cells in general have fewer intercellular contacts and fewer attachments to the stroma because action-to-membrane attachments are one of the prime targets of transformation-related disturbances.

JJ) **Altered intercellular communication.** Overall, it seems that decreased communication between cells favors cell proliferation: for example, mice lacking connexin32 (a gap junction protein of liver cells) spontaneously developed 8 times more liver tumors than control mice.

KK) communicating junctions also exist between the neoplastic cells of a given tumor.

LL) oncogene regulates intercellular communication and growth.

MM) Tendency to shed surface molecules, including proteins, glycoproteins, and enzymes (collagenase can help the malignant cell work its way through the extracellular matrix, fibronectin may lead to exaggerated clotting). Some of the shed molecules can be found in the blood and are therefore available as tumor markers, a useful device for diagnosing the presence of a particular type of tumor or for monitoring its response to therapy.

8. Effects of tumor on host

Cancers are far more threatening to the host than benign tumors are. Nonetheless, both types of neoplasia may cause problems because of location and impingement on adjacent structures, effects on functional activity such as hormone synthesis, and production of bleeding and secondary infections when the lesion ulcerates through adjacent natural surfaces. Cancers also may be responsible for cachexia (wasting) or paraneoplastic syndromes.

Location and size are crucial in benign and malignant tumors. A small (1-cm) pituitary adenoma can compress and destroy the surrounding normal gland and give rise to hypopituitarism. A 0.5-cm leiomyoma in the wall of the renal artery may lead to renal ischemia and serious hypertension.

Hormone production is seen with benign and malignant neoplasms arising in endocrine glands. Adenomas and carcinomas arising in the β cells of the islets of the pancreas often produce hyperinsulinism, sometimes fatal. Analogously, some adenomas and carcinomas of the adrenal cortex elaborate corticosteroids that affect the patient (e.g., aldosterone, which induces sodium retention, hypertension, and hypokalemia).

Ulceration through a surface with consequent bleeding or secondary infection needs no further comment.

Cancer cachexia. Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia. This wasting syndrome is referred to as *cachexia*. Usually an intercurrent infection brings an end to the slow deterioration. There is in general some correlation between the size and extent of spread of the cancer and the severity of the cachexia. Small, localized cancers are generally silent and produce no cachexia, but there are many exceptions.

The origins of cancer cachexia are multifactorial. Anorexia is a common problem in patients who have cancer, even those who do not have tumors of the gastrointestinal tract. Reduced food intake has been related to abnormalities in taste and in the central control of appetite, but reduced calorie intake is not sufficient to explain the cachexia of malignancy. In patients with cancer, calorie expenditure remains high, and basal metabolic rate is increased, despite reduced food intake. This is in contrast to the lower metabolic rate that occurs as an adaptational response in starvation. The basis of these metabolic abnormalities is not fully understood. Perhaps circulating factors such as TNF and IL-1, released from activated macrophages, are involved. TNF suppresses appetite and inhibits the action of lipoprotein lipase, inhibiting the release of free fatty acids from lipoproteins. A protein-mobilizing factor that causes breakdown of skeletal muscle proteins by the ubiquitin-proteosome pathway has been detected in the serum of cancer patients. In healthy animals, injection of this material causes acute weight loss without causing anorexia. Other molecules with lipolytic action also have been found. There is no satisfactory treatment for cancer cachexia other than removal of the underlying cause, the tumor.

Paraneoplastic syndromes. Symptom complexes other than cachexia that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the

elaboration of hormones indigenous to the tissue of origin of the tumor are referred to as *paraneoplastic syndromes*. They appear in 10% to 15% of patients with cancer, and it is important to recognize them for several reasons:

- They may represent the earliest manifestation of an occult neoplasm.
- In affected patients, they may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease and confound treatment.

The paraneoplastic syndromes are diverse and are associated with many different tumors. The most common syndromes are hypercalcemia, Cushing syndrome, and hypercoagulability. **Cushing syndrome** as a paraneoplastic phenomenon is usually related to ectopic production by the cancer of ACTH or ACTH-like polypeptides. The mediation of **hypercalcemia**, another common paraneoplastic syndrome, is multifactorial. Perhaps the most important factor is the synthesis of a parathyroid hormone-related protein (PTHrP) by tumor cells (squamous cell carcinomas of the lung). Although structurally PTHrP resembles parathyroid hormone, it can be distinguished from it by specific assays. Also implicated are other tumor-derived factors, such as TGF-α, a polypeptide factor that activates osteoclasts, and the active form of vitamin D. Another possible mechanism for hypercalcemia is widespread osteolytic metastatic disease of bone, but *it should be noted that hypercalcemia resulting from skeletal metastases is not a paraneoplastic syndrome*. Paraneoplastic syndromes may take many other forms, such as **hypercoagulability** leading to venous thrombosis and nonbacterial thrombotic endocarditis or the development of clubbing of the fingers and hypertrophic osteoarthropathy in patients with lung carcinomas. Still others are discussed in the consideration of cancers of the various organs of the body

Sometimes one tumor induces several syndromes concurrently. For example, bronchogenic carcinomas may elaborate products identical to or having the effects of ACTH, antidiuretic hormone, parathyroid hormone, serotonin, human chorionic gonadotropin, and other bioactive substances.

9. Host defense against tumor: tumor immunity

Malignant transformation, as has been discussed, is associated with complex genetic alterations, some of which may result in the expression of proteins that are seen as non-self by the immune system. The idea that tumors are not entirely self was conceived by Ehrlich, who proposed that immune-mediated recognition of autologous tumor cells may be a "positive mechanism" capable of eliminating transformed cells. Subsequently, Lewis Thomas and McFarlane Burnet formalized this concept by coining the term *immune surveillance* to refer to recognition and destruction of non-self tumor cells on their appearance. The fact that cancers occur suggests that immune surveillance is imperfect; however, the fact that some tumors escape such policing does not preclude the possibility that others may have been aborted. It is necessary to explore certain questions about tumor immunity: What is the nature of tumor antigens? What host effector systems may recognize tumor cells? Is tumor immunity effective against spontaneous neoplasms.

Tumor Antigens

Antigens that elicit an immune response have been shown in many experimentally induced tumors and in human cancers. They can be classified broadly into two categories: **tumor-specific antigens**, which are present only on tumor cells and not on any normal cells, and **tumor-associated antigens**, which are present on tumor cells and on some normal cells. Experimental studies and the study of tumor-infiltrating lymphocytes in humans have revealed an important role for CD8+ cytotoxic T cells (CTLs) in tumor immunity. As is well known, CTLs recognize peptide antigens presented on the cell surface by major histocompatibility complex (MHC) class I molecules.

Cancer-Testis Antigens. These antigens are encoded by genes that are silent in all adult tissues except the testis-hence their name. Although the protein is present in the testis, it is not expressed on the cell surface because sperms do not express MHC I antigens. Thus, for all practical purposes, these antigens are tumor specific.

Tissue-Specific Antigens. Antigens in this category are best considered differentiation-specific antigens, and they are expressed on tumor cells and their untransformed counterparts. Such antigens include melanocyte-specific proteins which are expressed on normal melanocytes and melanomas. Thus, cytotoxic T cells directed against these antigens would destroy not only melanoma cells but also normal melanin-containing cells.

Antigens Resulting From Mutational Change in Proteins. Antigens in this category are derived from mutant oncoproteins and cancer suppressor proteins. Unique tumor antigens arise from products of *RAS, TP53,* and *CDK4* genes, which frequently are mutated in tumors. Because the mutant proteins are present only in tumors, their peptides are expressed only in tumor cells.

Overexpressed Antigens. These tumor antigens are products of normal genes that are overexpressed because of gene amplification or other mechanisms. To this category belongs the HER-2 (neu) protein, which is overexpressed in 30% of breast and ovarian cancers. Although present in normal ovarian and breast cells, its level is generally too low for T-cell recognition.

Viral Antigens. Antigens derived from oncogenic viruses such as HPV and EBV can be targeted by CD8+ T cells. Such tumor antigens are shared between all tumors of similar type in different patients. They can be effective targets for immunotherapy because they are not expressed in normal cells.

Other Tumor Antigens. *Mucins* can give rise to tumor-specific antigens. In some cancers, such as those derived from pancreas, ovary, and breast, underglycosylation of mucins generates epitopes that previously were masked by carbohydrates. Therefore, these antigens, for all practical purposes, are tumor specific.

Oncofetal Antigens. Oncofetal antigens or embryonic antigens, such as carcinoembryonic antigen (CEA) and α-fetoprotein, are expressed during embryogenesis but not in normal adult tissues. Antibodies can be raised against these, and they are useful for detection of oncofetal antigens. These antigens serve as serum markers for cancer.

Differentiation-Specific Antigens. Differentiation-specific antigens, such as CD10 and prostate-specific antigen (PSA), are expressed on neoplastic and normal B cells and on benign and malignant prostatic epithelium, respectively. These serve mainly as diagnostic markers for the type of cell involved in transformation.

All this antigens may be used for early diagnostics of neoplasm.

Cell-mediated and humoral antitumor immunity

Cytotoxic T lymphocytes. The role of specifically sensitized cytotoxic T cells in experimentally induced tumors is well established. In humans, they seem to play a protective role, chiefly against virus-associated neoplasms. The presence of MHC-restricted CD8+ cells that can kill autologous tumor cells within human tumors suggests that the role of T cells in immunity against human tumors may be broader than previously suspected. They recognize antigens described earlier. In some cases, such CD8+ T cells do not develop spontaneously in vivo but can be generated by immunization with tumor antigen-pulsed dendritic cells.

Natural killer cells (NK) cells are lymphocytes that are capable of destroying tumor cells without prior sensitization; they may provide the first line of defense against tumor cells. After activation with IL-2, NK cells can lyse a wide range of human tumors, including many that seem to be nonimmunogenic for T cells. T cells and NK cells seem to provide complementary antitumor mechanisms. Tumors that fail to express MHC class I antigens cannot be recognized by T cells, but these tumors may trigger NK cells because the latter are inhibited by recognition of normal autologous class I molecules. The triggering receptors on NK cells are extremely diverse and belong to several gene families. They recognize stress-induced antigens that are expressed mainly on tumor cells. In addition to direct lysis of tumor cells, NK cells can also participate in antibody-dependent cellular cytotoxicity.

Activated **macrophages** exhibit selective cytotoxicity against tumor cells in vitro. T cells, NK cells, and macrophages may collaborate in antitumor reactivity because interferon-γ, a cytokine secreted by T cells and NK cells, is a potent activator of macrophages. These cells may kill tumors

by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen metabolites; or by secretion of tumor necrosis factor (TNF). In addition to its many other effects, this cytokine is lytic for several tumor cells.

Humoral mechanisms. These may participate in tumor cell destruction by two mechanisms:

JJ activation of complement and (2) induction of antibody-dependent cellular cytotoxicity by NK cells.

Immunosurveillance

Most cancers occur in individuals who do not suffer from any overt immunodeficiency. If immunosurveillance exists, how do cancers evade the immune system in immunocompetent hosts? Several escape mechanisms have been proposed:

Selective outgrowth of antigen-negative variants. During tumor progression, strongly immunogenic subclones may be eliminated.

Loss or reduced expression of histocompatibility antigens. Tumor cells may fail to express normal levels of human leukocyte antigen (HLA) class I, escaping attack by cytotoxic T cells. Such cells, however, may trigger NK cells.

Lack of costimulation. Sensitization of T cells requires two signals, one by foreign peptide presented by MHC and the other by costimulatory molecules; although tumor cells may express peptide antigens with class I molecules, they often do not express costimulatory molecules. This not only prevents sensitization but also may render T cells anergic or cause them to undergo apoptosis.

Immunosuppression. Many oncogenic agents (e.g., chemicals and ionizing radiation) suppress host immune responses. Tumors or tumor products also may be immunosuppressive. For example, transforming growth factor (TGF)-β, secreted in large quantities by many tumors, is a potent immunosuppressant. In some cases, the immune response induced by the tumor (e.g., activation of regulatory T cells) may inhibit tumor immunity. Another clever mechanism used by tumors is to express Fas ligand, which engages Fas on the surface of T cells and sends a death signal to the immune cells.

Also, we can find increased frequency of cancers in immunodeficient hosts. About 5% of individuals with congenital immunodeficiencies develop cancers, a rate that is about 200 times that for individuals without such immunodeficiencies. Analogously, immunosuppressed transplant recipients and patients with AIDS have increased numbers of malignancies.

10. The theory of tumor iniciation, promotion and progression

The concept that tumors develop by steps was born in the 1930s. Working on rabbit tumors produced by a virus or tar, Rous and his co-workers noticed that the path to malignancy was not a continuous slope. At first they obtained hyperplastic lesions that behaved as benign warts or papillomas; but then these papillomas did not become globally more and more atypical until they could be called cancers. Instead, most cancers arose quite suddenly and only in a part of a papilloma, as a wholly new and different event.

Intensive work on the multistep theory soon produced a dogma: tumor production occurs in two main phases, initiation and promotion, followed by a relentless, stepwise increase in malignancy called progression.

Initiation and Promotion

Initiation (or transformation) is characterized by the ability to transform healthy cells into cells with endless growth. Such ability can be the result of mutation or genome changes as a consequence of disregulatory processes. It is conceived as a quick, almost instantaneous process; if it

is repeated, the effect on the tissue is additive. Initiators can be chemical, physical, or biological. They do not cause cell proliferation. Initiated cells are morphologically indistinguishable from normal cells, at least to the present.

Promotion is the second stage in the mechanism of carcinogenesis. The transformed cells may remain in the tissue in inactive form for a long time. Additional influence of cocarcinogenic

factor stimulates cell reproduction and formation of tumor node. Promotion is viewed as a slow process; its effect is reversible and nonadditive. Many promoters cause cells to multiply; in fact, there is some consensus that hyperplasia is a typical effect of promoters. Some promoters have a certain degree of organ specificity

A puzzling fact had been reported off and on since the 1920s: if the skin of an experimental animal is painted with tar and then biopsied for microscopic study, tumors often arise at the site of the biopsy. The basic plan was to tar rabbit ears throughout a period somewhat less than is ordinarily required to elicit growths, and then to wound the ear. The results were clear; wounding was enough to encourage latent neoplastic cells. The tar had somehow initiated the neoplastic process, and the wound promoted it.

The principle of initiation by a subcarcinogenic dose was retained, but wounding as a promoter was replaced with a local irritant; the choice was croton oil. This technique of promotion became more scientific when two laboratories, one in Germany, the other in New York, independently isolated the irritating principle of croton oil and named it, respectively, phorbol myristate acetate (PMA) and tetradecanoyl phorbol acetate (TPA) the latter name seems to have won. Many other initiators and promoters were proposed, but the most popular of the promoters remains TPA

Eventually the basic rules of the initiation-promotion routine were worked out. To begin, promotion before initiation produces no tumors.

However, the theory of initiation and promotion has its flaws, as all theories do. It was derived largely from experiments based on painting mouse skin, a somewhat limited sample of carcinogenesis. Most carcinogens are initiators as well as promoters, a fact that is brushed off by deciding that these are complete carcinogens. Furthermore, some promoters can also produce tumors. Last, the initiation - promotion scheme requires a mutagen, whereas it is now well known that many cancers arise without mutagens. In essence, then, the facts appear to tell us that the initiation-promotion theory offers a satisfactory paradigm for interpreting some, and perhaps most cancers of the skin and other sites, but not all cancers.

Tumor progression

Progression is realized as stable qualitative changes of turner properties towards malignization.

Once malignant tumors have started to grow, they tend to go from bad to worse: this is how Rous and Kidd described in 1941 what is now called tumor progression, the third phase in the initiation-promotion-progression paradigm. The term implies a drive toward increasing malignancy of the tumor itself and of its metastases. The basic mechanism is thought to be a genetic instability of neoplastic cells. Progression is now understood more broadly as the effect of disturbances that may occur anywhere from chromosome to gene to DNA structure.

The role of clones in progression. After a single cell is transformed, new clones continue to appear; under constant evolutionary pressures, some cells are eliminated because of a biological disadvantage, others succeed because they are progressively less demanding of growth factors, less sensitive to drugs and X-rays, more invasive, more metastatic. The final result is a polyclonal tumor. These changes arise under the influence of several factors:

- Not one but several cells become involved into primary carcinogenic that promotes formation of law sublines of cells in the growing tumor. A constant selection of the most viable cells goes on in the growing tumor under the influence of the changing conditions of its growth (nutrition, blood supply and innervation).

- Change of genotype and phenotype of the cells resulting in progression may be connected with continuation of the effect of carcinogenic factors on the genome of tumor cells.
- Acquisition of new properties by tumor cells, which is connected with superinfection by tumor and non-tumor viruses.

11. Metastases

A metastasis is a secondary tumor that grows separately from the primary and has arisen from detached, transported cells. In essence, it is a colony of the primary tumor. The seed that starts a metastatic growth can be transported by the blood or lymph, or by fluid in tissue spaces. Metastases represent the most lethal expression of malignancy and the most important concern of the treating physician. By the time the diagnosis of cancer is made, over half of the patients already have microscopic metastases and will die of them, because there is, overall, little hope for cure at that stage.

Lymphatogenous Metastasis

Malignant cells are carried by the lymphatics to the regional lymph nodes. The belief that cancerous cells spread first to the regional lymph nodes—where their advance may be temporarily arrested by the immune response—is the rationale for radical surgery, which removes both the primary neoplasm and the regional lymph nodes to thereby eliminate the most likely sites of early metastases. Removal of lymph nodes is performed only for those neoplasms in which lymphatic metastasis is common, eg, carcinoma and melanoma.

Hematogenous Metastasis

Entry of cancerous cells into the bloodstream is believed to occur during the early clinical course of many malignant neoplasms. Most of these malignant cells are thought to be destroyed by the immune system, but some become coated with fibrin and entrapped in capillaries. Skeletal metastases are common in cancer of the prostate, thyroid, lung, breast, and kidney. Adrenal metastases are common in lung cancer.

Metastasis in Body Cavities (Seeding)

Entry of malignant cells into body cavities (eg, pleura, peritoneum, or pericardium) or the subarachnoid space may be followed by dissemination of the cells anywhere within these cavities; the rectovesical pouch and ovary are common locations for peritoneal metastasis in patients with gastric cancer. Cytologic examination of the fluid from these body cavities for the presence of malignant cells is an excellent method of confirming the diagnosis of metastasis.

Dormancy of Metastases

Cancerous cells that spread to distant sites may remain dormant there (or at least remain slowly growing and undetectable), sometimes for many years. The presence of such dormant cancerous cells (or slowly growing subclinical metastases) has led to attempts to eradicate them by means of systemic chemotherapy after treatment of the primary tumor. While results have been encouraging in some types of disseminated cancer, including malignant lymphoma, choriocarcinoma, and testicular germ cell tumors, the overall cure rate is so low—and the morbidity of chemotherapy so high—as to question the validity of this approach for most malignant tumors.

Development of delayed metastases makes it difficult to pronounce a patient cured with any confidence. Survival for 5 years after treatment is considered a sign of cure for most cancers. However, 10- and 20-year survival rates are almost always lower than the 5-year survival rates, which suggests that many patients experience late metastases.

The metastatic cascade

From the point of view of the malignant cell, invasion and metastasis require the ability to overcome a series of obstacles, which have been aptly compared to a decathlon, named the metastatic cascade. To produce a hematogenous metastasis a cell must separate itself from the tumor mass and move in the right direction; it must digest its way through the intercellular matrix, and then through a vascular basement membrane to penetrate the lumen of a vessel; once there, it must escape the various defensive systems of the blood, including antibodies, complement, macrophages, killer cells of various sorts, oxygen, and even blood clotting; when it reaches a vessel small enough to be embolized, it must survive the impact and the mechanical squeeze; then it must proceed in revetse, penetrate the endothclium and the basement membrane, escape a new set of dangerous cells (macrophages,

lymphocytes), multiply, induce angiogenesis, and finally establish a tumor. In view of all these difficulties, it is not surprising that many tumor cells fail. At each step of

the metastatic cascade the metastatic cells are selected by a basic principle: survival of the fittest, which contributes to the phenomenon of tumor progression.

Genetic control of metastasis

A human gene, KiSS-1, encodes a peptide (metastin) that reduces the number of pulmonary metastases of a melanoma in the mouse. Most interestingly, metastin is abundant in the human placenta.

Data are available for all the steps of the metastatic cascade.

(1) Detachment

There is no question that malignant cells become detached from the tumor mass because they can be found in the bloodstream, single or in clusters.

Complete detachment from their neighbors may be due to

1.proteolytic enzymes diffusing outward from the necrotic core of the tumor.

2.their adhesion molecules are not properly expressed.

3.Active motility of tumor cells could also favor the detachment process, and there is ample proof that many types of malignant cells do show ameboid motion.

(2) Invasion

The interface between tumor and host is currently visualized as a zone of intense enzymatic activity: a band of matrix soaked in enzymes and their products, as well as growth factors and other cytokines. The malignant cells must digest their way through this gelatinous layer, using **heparanase** and **collagenase** specific for collagen fibrils and for basement membranes; they do so in part by appropriating stromal enzymes and using them mounted on their own surface. The enzymes critical for tumor invasion are **metalloproteases**. Mixed with these enzymes are their products, which can affect many different processes and thereby greatly complicate the issue. Growth pressure might be exploited by cancer cells forcing their way into the surroundings, but it cannot be the only mechanism. Active motility of cancer cells is well proven. It was calculated as far back as 1916 that the speed of cells observed in vitro would enable malignant cells to crawl from the breast to the axillary lymph nodes in 4 weeks.

(3) Penetration into the Blood Vessels

It should be basic three-step mechanism: attachment, lysis, and invasion. When tumor cells reach the perivascular basement membrane, they attach to it by means of laminin receptors (laminin is an adhesive molecule that reinforces basement membranes); then the tumor cells secrete collagenase (type 4), specific for the collagen of the basement membrane, and eventually move through. Tumor cells may not always need this arsenal: vessels in tumors are often defective and may lack basement membrane or the invading cell may punch its way through an endothelial cell, creating a temporary migration pore.

(4) Transport in the Bloodstream

Tumor cells are found in the blood of experimental animals as well as in humans. In humans it has been found repeatedly that trauma, including surgery, sends showers of tumor cells into the bloodstream. The number rarely exceeds 1000 per milliliter. There is no correlation between circulating cancer cells and number of metastases. Hazards encountered by tumor cells in the blood are many: coating with antibodies followed by lysis with complement, encounters with killer cells of various kinds and, according to recent studies, exposure to a toxic concentration of oxygen. The only possible advantage for the tumor cell might be the coating with platelets, which in some experimental systems seems to help the metastatic process. And then, within seconds of gaining entry into the bloodstream, tumor cells face the trauma of embolization, which can be their demise.

(5) Embolization Followed by Cell Death

Most tumor cells injected intravenously are killed by biomechanical trauma in minutes. The mechanical impact of embolism is fatal to many tumor cells because they are larger and less deformable than leukocytes. Biomechanical trauma must be especially severe in the heart where

capillaries receive a hefty squeeze at every beat, i.e., more than once per second. Similar effects apply to skeletal muscle.

(6) Embolization Followed by Growth

The embolic episode has been recorded cinematographically in vivo, quite a technical feat. It was shown that some tumor cells survive embolic trauma and continue to circulate.

The malignant cell or cluster settles in a capillary or precapillary vessel where it is always tightly apposed to the endothelial surface; it is often associated with platelets (which may act as a supply of growth factors) and with some strands of fibrin. Within a few hours the malignant cell (be it isolated or part of a cluster) sends a pseudopod between the endothelial cells or through them and makes contact with the basement membrane, while flow may resume. Thereafter the cell may exit from the vessel and pursue its career outside or divide and grow into a metastatic lump that occludes the lumen. The diapedesis of a tumor cell appears surprisingly similar to that of a leukocyte. New vessels may begin to sprout toward the metastasis after 24 hours, and a tumor vascular network is visible at 4 days. The production of **tumor angiogenesis factor** (TAF) by the cancerous cells stimulates growth of new capillaries in the vicinity of tumor cells and encourages vascularization of the growing metastasis. The site of metastasis is most commonly the first capillary bed encountered by blood draining the primary site. Some types of cancer apparently favor particular metastatic sites, although the mechanisms responsible are unknown.

12. Treatnent of neoplasms

The purpose of accurate diagnosis of the specific tumor type is to enable the clinician to select an appropriate mode of therapy. Even with the best treatment, survival rates vary greatly for different types of neoplasms.

Surgery is the most effective variant of neoplasia treatment. **For b**enign neoplasms surgical removal is curative. In a few cases, surgical removal may be difficult because of the location, eg, choroid plexus papillomas in the third ventricle. Surgical treatment of malignant neoplasms is more difficult because they tend to infiltrate tissues. Local excision requires careful pathologic examination (including frozen sections as required) of the margins of resection to ensure complete removal. For low-grade malignant neoplasms, wide local excision is frequently sufficient for cure. Incomplete removal leads to local recurrence. Malignant neoplasms with a high risk of early lymphatic metastasis are often treated by removal not only of the affected tissue but also of the lymph node group of primary drainage (radical surgery); in radical mastectomy, the axillary lymph nodes are dissected and removed with the breast.

Surgery alone is of little value when widespread metastases are present. However, surgical removal of isolated metastases may reduce tumor bulk, thereby enhancing the effects of chemotherapy and any residual immune response.

Radiation Therapy

Many malignant neoplasms are sensitive to radiation. In general, the more rapidly growing the neoplasm, the more likely it is to be radiosensitive; however, sensitivity is not synonymous with cure. The effect of radiation in a given neoplasm can be predicted on the basis of past experience with radiation therapy in similar neoplasms.

Chemotherapy

Advances in cancer chemotherapy have greatly improved the outlook for many patients with cancer. Chemotherapy is the treatment of choice for many neoplasms such as malignant lymphoma and leukemia. Anticancer drugs act in one of several ways: (1) by interfering with cell metabolism and ribonucleic acid (RNA) or protein synthesis (antimetabolites); (2) by blocking deoxyribonucleic acid (DNA) replication and mitotic division (antimitotic agents); or (3) by exerting hormonal effects, eg, estrogens in prostate carcinoma and antiestrogenic agents such as tamoxifen in breast carcinoma.

Immunotherapy

Attempts to stimulate the immune system with adjuvants such as bacille calmette-guérin [vaccine] (BCG) have met with limited success. More specific immunotherapy using monoclonal antibodies developed against tumor-associated antigens has been used in the treatment of malignant melanoma, lymphoma, and some carcinomas. One promising approach uses the antibody to carry cytotoxic drugs, toxins, or radioisotopes to the tumor site.

EXTREME CONDITION

During the life of a person can be exposed to various exogenous and endogenous factors of extreme force, duration and / or unusual, unusual character. The action of extreme factors leading to the development of an emergency or to adapt to this factor, or extreme, critical, urgent status.

Urgent adaptation is characterized by limiting the body's stress adaptation mechanisms that prevents the shift of the most important parameters and constants of its life beyond the normal range. The content of the state of emergency is the first stage adaptation of the adaptation process. Upon termination of the emergency factor, eliminate or compensate for its effects to normal body condition.

Extreme, critical, urgent condition characterized by significant impairment of vital activity, in spite of the limit activation mechanisms of adaptation. Independent exit the body of such a state, as a rule, is not possible. In such cases it is necessary to provide timely and effective medical care.

EXTREME AND TERMINAL STATES

Extreme conditions - severe general condition of the body, developing under the influence of extreme factors of the external or internal environment characterized by significant disturbances of vital activity, fraught with death.

Extreme conditions occur, as a rule, limiting the activation and subsequent depletion of coping mechanisms, rude disorders of functions of organs and physiological systems.

Extreme conditions require emergency medical care.

The most common and clinically important urgent conditions include collapse, shock, coma and poisoning.

From extreme is necessary to distinguish the terminal state, which represent the final stages of life of the organism, the borderline state between life and death.

terminal states

By the terminal states include all the stages of dying - preagonia, agonia, clinical death, as well as the initial stage of the state after a successful resuscitation.

Terminal states are usually the result of unfavorable course of extreme conditions. If the terminal is not able to carry out intensive medical measures or they are ineffective, it comes, and then the clinical - biological death.

The pathogenic factor → Extreme condition → terminal condition → Clinical Death → biological death

Extreme and terminal condition have both similar and radically distinguish their features. The similarity of extreme and terminal states

Extreme and terminal states have a number of common features:

4. Common causes.
5. Similar key pathogenesis.
6. Borderline situation between life and death.
7. Lead to the death of the organism.
8. Require urgent medical care.

Although there were similarities, the two states are qualitatively different groups from each other.

At the heart of the terminal states are much more severe and therefore prognostically unfavorable processes. If not carried out emergency remedial measures, the terminal state of

becoming progressive, irreversible flow, leading to death. In contrast, under certain extreme conditions (collapse, and sometimes - in the early stages of shock) can activate the processes of adaptation, reducing the degree of deviation of homeostasis parameters, improving the body's ability to live in and out of these states.

When development terminal state gradually lost its importance of nature caused the causal factor. Pathogenic effects of his actions are so great that the specific reasons for the state of the terminal loses its meaning.

Specificity is low and terminal states of development mechanisms. When different types of these states key links of their pathogenesis are hypoxia, abnormalities of acid-base balance, blood gases, toxemia, and others. In contrast, under extreme conditions identified as the specifics of the calling their agent, and especially their development mechanisms. In this regard, for specific causal and pathogenetic therapy of extreme conditions can block their development and normalize the functioning of the organism.

General etiology of extreme conditions

Extreme factors different from other pathogenic agents that provide the data and the specific conditions under the action of the body is very high, very intense, often devastating effect.

Types of extreme factors.

Extreme factors are divided into exogenous and endogenous.

1. extreme exogenous factors may be physical, chemical or biological nature.

- Factors of the physical nature: mechanical, electrical, thermal, barometric, radiation, gravity.
- Chemical factors: limiting the deficit / surplus of oxygen, metabolic substrates, liquid; expressed intoxication of drugs, industrial poisons, acids, alkalis.
- Biological factors: significant deficit / surplus of exogenous bioactive substances; bacteria, parasites and fungi (toxins, metabolic products thereof, and / or decay).

2. Endogenous (adverse, severe course of disease and disease states).

- Severe impairment of functions of organs and physiological systems.
- A significant blood loss.
- Massive bleeding in the organs.
- Excess food or allergic immune responses.
- A significant deficiency / excess of BAS and / or their effects.
- Mental surge injury.

Conditions that contribute to extreme conditions.

1. Factors potentiating effects extreme agents.

For example, the state of sensitizing the body can lead to a more severe course of anaphylactic shock by the action of the allergen, the effects of blood loss are compounded at elevated temperature, heart failure when performing excessive exercise can lead to cardiogenic shock, etc.

2. The reactivity of the organism.

Often it is a decisive condition for the action of extreme factors. Unlike normergic response hypo - or hyperergic condition of the body facilitates the occurrence, course and outcomes exacerbating extreme condition.

Pathogenesis of extreme conditions

Extreme conditions are characterized, as a rule, dynamic stage development. In most cases (except for acute and quickly developing situations caused by extreme superstrong factors leading to rapid death of the body) in the dynamics of increasing severity of extreme conditions can be

divided into three stages: the activation of adaptive mechanisms, exhaustion and lack of them, extreme regulation of the body's vital functions.

Stages of extreme conditions.

Stage 1: Activation of adaptive mechanisms

The reason - the alarm action:

3. damaging factor,
4. deviations of the parameters of homeostasis **Stage 2:** Failure of adaptive mechanisms Causes:
6. increase the degree and extent of damage of the organism,
7. stress and exhaustion of adaptive processes **Stage 3:** Extreme regulation of vital activity Causes:

6) a further increase in the extent and scale of the body damage,
7) progressive failure of adaptive mechanisms.

Stage activation of adaptive mechanisms of the organism

This stage is characterized by a generalized activation of the legitimate functions of tissues, organs and systems. This is the basis of development of adaptive reactions of varying degrees of severity and specificity. Essentially all of these reactions can be divided into two categories:

JJ. Providing specific adaptation to the particular extreme factors;

KK. Implement the non-specific, standard processes, developing under the influence of any extreme effects, ie stress reaction.

Stage failure of adaptive mechanisms

The main feature of this stage: the lack of efficiency of adaptive responses and growth of the damaging effect of extreme agent.

1. Pathogenesis

6. Increasing the efficiency of reduction reaction devices, compensation, protection and reparation.
7. Progressive disorder of the physiological functions and the collapse of the functional systems of the body.
8. Metabolic disorders and physical-chemical processes.
9. Damage to the structural elements of organs, tissues and cells
10. Braking plastic processes them.

As a result of these changes most homeostasis parameters deviates beyond the normal range, and often significantly. Vital functions of the whole organism is disturbed significantly.

2. Vicious circles

With all the extreme states, albeit with a different frequency, can form a vicious circle. This phenomenon lies in the fact that an initial pathogenetic factor causes a closed complex by increasing the degree of violation. Consequences of them, in turn, potentiate the action of an initial pathogenic factor based on positive feedback.

3. Education pathogenetic vicious circle leads to growth disorders in the body, "weighting" extreme conditions up to move it to the terminal, even in the termination of extreme factors.

examples:

4. During the collapse, shock and coma observed blood flow redistribution. A large amount of blood is collected in the extended venous and arterial vessels of the abdomen, lungs, subcutaneous tissue. This significantly reduces the bcc and hence the blood flow to the heart. The consequent decrease in cardiac ejection of blood leads to an even greater decrease in VCB and exacerbate the patient's condition.

5. Activation phenomenon lipoperoxide processes in tissues. Hypoxia, growing in all types of extreme conditions, results in the suppression of the activity of non-enzymatic and enzymatic

antioxidant defense system tissue. This leads to intensification of education in which reactive oxygen species and lipoperoxide processes that damage the enzymes of tissue respiration, glycolysis, the pentose phosphate shunt. The latter is even more aggravated hypoxia - a vicious circle and potentiating its development.

In general, at the stage of failure of adaptation mechanisms in various extreme states is developing a set of regular stereotypical interrelated changes in the body. For chief among them are the characteristic triad of disorders.

4. Frustration and lack of functions of organs and physiological systems: the neuro-humoral, respiratory, cardiovascular, blood, hemostasis, and others.
5. Significant abnormalities of homeostasis parameters, including essential and critical.
6. Damage to the subcellular structures, cells and disruption of intercellular interaction.

Manifestations.

Disorders of the nervous system. They are characterized by different degrees of sensitivity and character disorders, motion control, integration of activity of bodies, tissues and systems, VNS.

- In the collapse (due to significant violations of perfusion of organs, including the brain) develops a condition characterized by indifference to events, the oppressed and the deep anguish.

- When shock conditions (in the braking phase) showed a significant inhibition, detachment, "leaving a" loss of contact with others.

- In a coma consciousness violated. First, there is confusion and drowsiness, and soon - loss of consciousness, combined with hyporeflexia. At the same time revealed significant disorders of blood circulation, breathing and other vital functions. The latter is a result of integrating function disorder of the nervous system.

Violation of the CVS activities. Manifested arrhythmias and signs of coronary heart disease, various disorders of the central, organ, and microcirculation. This leads to the development of capillarotrophic failure in various organs. This in turn potentiates the failure of their functions - heart, kidneys, liver, lungs, and others.

Variations in the blood system and hemostasis. Causes a violation of the volume, viscosity and flow of blood; forming units of its formed elements, the phenomenon of sludge, blood clots. A frequent consequence of hemostasis disorders are trombohemorragic state, often leading to death of the organism.

Disorders of external respiration. Exacerbate extreme conditions due to the potentiation of hypoxemia, hypercapnia and hypoxia. At the stage of failure of adaptation mechanisms, tend to develop so-called periodic breathing forms (Biota, Cheyne-Stokes, Kussmaul), while during heavy - its complete cessation - apnea.

The lack of kidney function. It appears oligo - or anuria, filtration disorder, excretion, secretion and other processes in them. This often leads to varying degrees of severity of uremia.

Violation of the liver. Causes the disorder of protein, carbohydrate and lipid metabolism, metabolism of bile pigments, the inactivation process of toxic metabolic products, potentiates hemostatic disorders. At the duration of the current extreme conditions (eg, coma), severe liver failure can significantly speed up the transition to the terminal.

Disorders of the functions of the digestive tract. Develop, as a rule, in case of severe during these extreme conditions such as shock and coma. They manifest violations of the secretory and motor functions of the stomach and intestines (until his paresis), cavity and membrane digestion. Therefore patients often develop autoinfection intestinal syndromes, auto-intoxication and malabsorption.

Significant deviations from the normal range of homeostasis parameters. It is a natural manifestation of the failure of functions of organs and systems. The most significant variations:

a) Reduction of the partial voltage and the oxygen content in the blood. This indicates the development of hypoxia, which is on the rise as well as severity of the condition progresses.

- Hypoxia in almost all varieties of extreme conditions plays a very important, and in many cases - a major pathogenic role, being one of the key and obligatory links of their pathogenesis.

- The origin of hypoxia, is usually mixed. It is caused by disorders of the central, organ, tissue and microcirculation, external and tissue breathing process of oxygenation of hemoglobin in the lungs and its dissociation in the tissues, as well as deficiency of substrate oxidation.

- During the development of the state of extreme hypoxia causes or potentiating factor cascade of disorders defined by it: acidosis, the intensification of the processes of generation of reactive oxygen species and lipoxide, imbalance and other ions.

b) Reduction of the pH of blood plasma and other biological fluids (acidosis development). Acidosis may be a gas (respiratory) and non-gas (metabolic and excretory).

c) Abnormal content of different ions. The breakdown of biological oxidation in the tissues and as a result - their energy and acidosis cause a violation of physico-chemical state of cell membranes and enzymes. This leads to the intracellular accumulation. Na +, Ca2 + and other ions exit the cell K +, Mg2 +, H +, trace elements. Therefore the optimal ratio of the ions is disturbed between cells and body fluids. Excess hydrophilic Na + in cells causes their overhydration, swelling and, frequently, the membranes rupture.

d) Changes in the value of the MP and PD characteristics of the surface charge of cells, their colloidal state plasmolemma and cytosol, the osmotic pressure of blood plasma.

9. Changes in the body at the stage of failure of adaptation and reaction mechanisms of extreme conditions may differ significantly for different kinds of (collapse, shock, coma) and even with the same form, but in different patients. The reason is that the original disorder functions, metabolism, plastic processes and structures cause a cascade of secondary violations.

Stage extreme regulation of vital activity

The main characteristics of the stage of extreme regulation of the body's vital functions.

Hypo - and deafferentation:

- Central nervous structures,

d) Organs and tissues.

↓

Lack of functions and the collapse of the physiological and functional systems

↓

Minimization:

4) The functions of organs and tissues,

Energy expenses,

Plastic processes.

↓

Metabolic regulation of the functions of organs and tissues

↓

The terminal condition

The reasons: the growth of the degree and extent of damage to the body, progressive failure of adaptation mechanisms.

Pathogenesis

Key pathogenesis:

5) Increasing (with a significant energy shortage, acidosis, disorders of the ion balance and other changes in the body), hypo - and deafferentation of the central and peripheral nervous structures, as well as the executive organs and tissues.

6) The collapse of functional systems that maintain the body's vital parameters.

7) The transition to elementary - level metabolic regulation of vital functions of organs and tissues.

With an increase of these changes is developing a terminal condition and death occurs. However, holding on extreme control stage effective treatment can block the progression of the disorder, restore and even normalize the condition of the victim.

PRINCIPLES OF TREATMENT OF EXTREME CONDITIONS

mmediate therapeutic measures when extreme conditions are based on the implementation of the four basic principles: etiotrop, pathogenetic, and symptomatic sanogenetic.

Etiological treatment

Causal treatment is designed to stop or decrease the strength and scale of pathogenic action adventure agent. This is achieved by different methods depending on the type of emergency conditions.

For example:

NN Stop the bleeding;
OO Termination of the low or high temperature;
PP Normalization of the oxygen content in the inspired air;
QQ Elimination of failure, organ function, hormone deficiency or their effects;
RR The use of antitoxic means.

Pathogenetic treatment

Pathogenetic therapy aims to block the development of mechanisms for extreme conditions. This objective is usually achieved by acting on the key or key binding pathogenesis. These include circulatory disorders, respiratory depression, hypoxia development, shifts AAR, ion imbalance, activation processes lipoxigenic and others.

Sanogenetic therapy

Sanogenetic therapy aims to activate and / or potentiation of defense mechanisms, compensation, adaptation and compensation for lost or damaged structures and functions of the body. Ensured by stimulation of the heart function, respiratory, kidney, liver and other organs and tissues; activation of repair processes of detoxification systems, the elimination of excess oxygen radicals and lipid; potentiation of plastic and other reactions.

Symptomatic treatment

Symptomatic therapy involves the removal of unpleasant, painful, aggravating the condition of the patients symptoms and sensations: headaches, fear of death, causalgia, hypo- or hypertensive reactions and others.

In addition to the implementation of the general principles of the above-described treatment of extreme conditions, in each patient carried a set of individual measures, taking into account the specific characteristics of extreme exposure, especially to respond to him of the victim, the dynamics of life and severity of disorders, moreover, a particular version of an extreme condition.

Collapse

Collapse - general, developing acute condition that occurs as a result of significant discrepancies bcc capacity of the vascular bed. It is characterized by circulatory failure, the primary circulatory hypoxia, a disorder of functions of tissues, organs and systems.

Species origin collapse

Cardiogenic	Hypovolemic	vasodilatory
- Myocardial	- posthemorrhagic	- hyperthermal
- Arrhythmic	- dehydration	- toxic
- cardiomiopathic	- toxic and infectious	- orthostatic
	- orthostatic	

ETIOLOGY

The immediate cause of the collapse is a rapidly developing significant excess capacity of the vascular bed in comparison with VCB.
The reasons for the collapse of

By reducing the value of blood ejected from the heart ventricles in the vascular bed develops cardiogenic collapse. This occurs when:

3. Acute heart failure (caused by ischemia and myocardial infarction, significant Brady - or tachycardia);
4. Conditions that impede the flow of blood to the heart (with stenosis of the valve hole, embolism or vascular stenosis of the pulmonary artery system);
5. There are obstacles to eject blood from the left ventricle (the most common in stenosis of the valve opening of the aorta).

2. When reducing the BCC develops hypovolemic collapse. By this result:

6. Acute massive bleeding;
7. Rapid and significant dehydration (with profuse diarrhea, poisoning, sweating, uncontrollable vomiting);
8. The loss of a large volume of blood plasma (for example, extensive burns);
9. Redistribution of blood from the deposit large amounts of it in the venous blood vessels, blood capillaries and sinuses (eg, in shock, gravitational overloads, some intoxication).

3. By reducing the total peripheral vascular resistance develops vasodilatory collapse. This can occur in severe infections, intoxication, hyperthermia, endocrinopathy (with hypothyroid conditions, acute and chronic adrenal insufficiency), incorrect use of drugs (eg, sympatholitic, ganglioblockage, drugs, calcium channel blockers), hypocapnia, blood excess adenosine, histamine, kinins, profound hypoxia and a number of others.

Risk factors

Collapse development is largely dependent on a number of specific conditions (risk factors):

5. Physical characteristics of the environment (low or high temperature, level barometric pressure, humidity);
6. The state of the body (the presence or absence of a disease, pathological process, psycho-emotional status, etc.).

These and other conditions can both promote and impede the emergence collaptoid nature, as well as a significant effect on the severity of its course and outcome.

Types of collapse

In addition to the most common - cardiogenic, hypovolemic and vasodilatory collapse in the practice of medicine frequently isolated species collapse, taking into account its specific cause or group of related reasons: posthemorrhagic, infectious, toxic, radiation, pancreatic, orthostatic, hypocapnic and others.

GENERAL PATHOGENESIS AND MANIFESTATIONS COLLAPSE

Violation of the functions of the CAS is an initial and main pathogenetic link of collapse and is characterized by inadequate blood supply to organs and tissues. Typical of these circulatory disorders:

5. Reduced stroke volume and cardiac output;
6. Acute hypotension;
7. Venous congestion;
8. The redistribution of blood flow (blood deposition in the capacitance vessels of the abdomen, lungs, spleen and brain hypoperfusion, heart and other organs);
9. Violation of the microcirculation of blood and lymph;
10. The development of capillary-trophic failure.

- The disorder of the nervous system. It has an important pathogenetic significance. The collapse is usually accompanied by:
- Lethargy;
- Apathy, indifference to what is happening; - Tremor of the fingers;

8) Sometimes convulsions;
9) Hyporeflexia;
10) Syncope with significant hypoperfusion and cerebral hypoxia.

SS Violations of the gas exchange function of the lungs. This is evidenced by: - Frequent and shallow breathing;
- Hypoxemia;
- Hypercapnia in the blood flowing from the lungs.

TT The breakdown of the excretory renal function. Given that the collapse of the system is characterized by acute arterial hypotension and therefore - renal hypoperfusion, patients often detected:
- Oliguria; - Baruria;
- Hyperasotemia.

UU Disorders of blood and hemostasis systems:
10. Hypovolemia;
11. Increase in blood viscosity (in connection with the release of its liquid part through the walls of blood vessels, the permeability of which is increased under conditions of hypoxia);
12. Hyperaggregation platelets and red blood cells;
13. Blood clots;
14. The development of the phenomenon of sludge.

Many of the above symptoms of collapse caused by the development of hypoxia, circulatory initially, and subsequently mixed (including respiratory, hematic, fabric, substrate). With increasing severity of hypoxia may develop significant disturbances of vital activity, fraught with death.

FEATURES OF CERTAIN COLLAPSE

Despite the similarities of the pathogenesis and manifestations of various kinds of collapse, some of which have significant differences.

Hemorrhagic collapse

An initial pathogenetic factor hemorrhagic collapse - a rapid and significant decrease in the bcc (hypovolemia). The increase in this context of vascular tone does not eliminate the disparity of their capacity to significantly reduce the BCC. As a result, developing hypoperfusion of organs and tissues. This leads to increasing initially circulatory and then mixed (hemic, tissue) hypoxia. The consequence of hypoxia is a progressive disorder of the nervous system, lungs, kidneys, etc.

To replenish the lost blood (mainly its formed elements by activating hematopoiesis) takes a few days (in severe cases, not less than 7-12 days); therefore (bicarbonate, etc.) to eliminate

hemorrhagic collapse and its consequences require urgent administering to the calculated amount of whole blood, red cells, plasma expanders, solutions containing the necessary quantity of ions and buffer system components.

Orthostatic collapse

An initial element of the pathogenesis of orthostatic collapse (fainting) - systemic vasodilatation resulting in a sharp decrease in arteriolar tone walls and capacitive vessels. There is a sharp transition of the body in a vertical position from lying or sitting position, especially after prolonged inactivity. This results in the activation of cholinergic effects on vascular walls due to the stimulation of the neurons of the vestibular centers with a sudden change in body position.

An important risk factor, and then the pathogenetic link orthostatic collapse - reduction of reactive properties of the resistive vessel walls to vasopressor agents: catecholamines, angiotensin, etc. One of the major reasons for this may be adrenal insufficiency (warrant the deficiency of catecholamines and corticosteroids), upset kardiovazomotornogo center functions and hypothalamus (causing violation of the tone of the vessel walls) and some others.

Toxic-infectious collapse

The cause of toxic and infectious collapse: the pathogenic effects on the body toxins exogenous and endogenous origin of infectious or non-infectious nature (microbial toxins and parasites in their massive destruction, for example, as a result of antibiotic treatment, the products of disturbed metabolism, phosphorus compounds, carbon monoxide and many other).
Toxins are responsible for:

7. Direct neuro, cardio and myotropic damage;
8. Metabolic disorders and the implementation and effects of vasopressor agents vasodepressor;
9. Disorders of mechanisms of regulation of vascular tone and cardiac activity.

As a result of growing expressed in varying degrees of decreased tone of resistive vessels, cardiac output, VCB.

With a significant and progressive decrease of these indicators are observed rapidly growing life of the organism disorder and poses a threat to his life.

METHODS OF TREATMENT OF COLLAPSE

The therapy is based on the realization collapses etiotropic, pathogenetic, and symptomatic sanogenetic principles. The result of the treatment of the collapse is largely determined by how much time has passed from the appearance of signs of collapse before the start of therapy: the shorter the period, the lower the degree of disorders of vital functions and the effectiveness of therapy.

Etiotropic treatment

Measures are taken to stop the action of extreme factors and / or reduce the extent of its damaging influence: stop bleeding, injected antitoxin, antidotes, anti-microbial drugs, and others.

Pathogenetic therapy

This is achieved by eliminating or reducing the degree of the effects of non-compliance capacity of the vascular bed, and bcc. For this purpose, patients infused blood products, shelter - or plasma expanders, buffers; administered drugs that increase the tone of the walls of the resistive and capacitive vessels, activating function of the heart and respiratory center; oxygen therapy is performed by inhalation of gas mixtures with high oxygen content or partial hyperbarotherapy; if there are signs of adrenal insufficiency using corticosteroids.

Sanogenetic therapy

Sanogenetic principle of collapse therapy involves the stimulation of adaptation mechanisms: the activation of the hematopoietic-specific and non-specific factors and processes IBN system, detoxifying the liver and other functions, excretory capacity of the kidneys, and others.

Symptomatic therapy

Symptomatic treatment includes measures to eliminate the painful, unpleasant and aggravating the patient's condition manifestations of collapse:. Pain, fear of death, depression, anxiety, etc. To this end, (depending on the specific situation) used antidepressants, antipsychotics, sedatives and painkillers, stimulants, tranquilizers.

Shock

Shock - overall, an extremely heavy condition of the body that occurs under the influence of super-strong extreme factors. Characterized by-step progressive disorder of the body's vital functions as a result of the increasing dysfunction of the nervous, endocrine, cardiovascular and other vital systems.

Output patient of the shock state can usually only during medical emergency and effective measures. Without this shock usually results in a terminal state.

ETIOLOGY SHOCK

An important feature of shock is that it causes extreme high power factor, usually leading to extensive destruction of various structural elements of the tissues and organs.

Causes

11. Different versions of injury (mechanical damage - the destruction, breaks, break, crush tissues, extensive burns, electric shocks, etc.).
12. Massive blood loss (as a rule, combined with the injury).
13. Large volume transfusion of incompatible blood.
14. Contact with the internal environment of the body sensitized to allergens.
15. Significant extensive necrosis or ischemia organs (heart, kidney, liver, intestines and others.).

Risk factors

For conditions, potentiating the action of extreme factors and promote the development of shock include:

- Hypothermia and hyperthermia,
- Prolonged fasting,
- Nervous and mental excitement,
- Significant physical fatigue,
- General hypo - or hyperergic state
- Chronically proceeding severe disease.
- Individual reaction to this extreme exposure. Practice is rich in cases of shock in a relatively small injury and at the same time the lack of shock at the massive damage to the body.

TYPES OF SHOCK

A common classification of shock there.

The criterion for differentiation states of shock mainly serves the cause. With this in mind, the most common and clinically important types of shock include traumatic shock (wound), burns,

post-transfusion, allergic (anaphylactic), electric, cardiogenic, toxic, psychogenic (psychological) and others.

In practical medicine shock states are divided depending on the severity of their course: the shock of I degree (light), shock II degree (moderate severity), III of the degree of shock (heavy).

GENERAL PATHOGENESIS AND MANIFESTATIONS STEPWISE SHOCK

Regardless of the severity of clinical manifestations distinguish two successive stages of developing shock.

3. First, there is the activation of specific and nonspecific adaptive reactions. This step was previously called the stage of generalized excitation, or erectile. In recent years, it is called adaptive, compensatory, non-progressive, early.
4. If the adaptation processes are insufficient, developing the second stage of shock. Previously, it was called the total braking stage, or torpid (from the Latin torpidus -. Sluggish). At present time it is called stage deadaptation or decompensation. At this stage, identify two substage: progressive (consisting in the depletion of compensatory reactions and tissue hypoperfusion) and irreversible (in the course of which develop changes that are not compatible with life).

Erectile stage

Stage erectile (compensation, non-progressive, adaptation) is the result of significant severity and scale of the damage to the organs and tissues of extreme factors, as well as emerging under his influence, secondary changes in the body.

The basic pathogenesis of shock at the stage of compensation:

Neuroendocrine link

Excessive generalized activation of the nervous and endocrine systems, developing in connection with hyperafferentation different modalities, is characterized by a significant increase in effector effects on organs and tissues from the sympathetic-adrenal and hypothalamic-pituitary-adrenal system, the release into the blood hormones of the thyroid, pancreas and other endocrine glands.

The result is a hyperactive CVS and respiratory system, kidneys, liver and other organs and tissues. Implication:

4. Hypertensive reactions
5. Tachycardia,
6. Increased and deepening of breathing,
7. Redistribution of blood flow in different regions of the vascular bed,
8. The release of the blood from the depot.

These reactions are adaptive directionality. They provide in conditions of extreme factor delivery to the tissues and organs of oxygen and substrate metabolism, maintaining perfusion pressure.

With increasing degree of damage, these reactions take excessive, inadequate and uncoordinated nature, which greatly reduces their effectiveness. It determines to a large extent or even irreversible heavy aggravate during states of shock.

Consciousness is not lost in shock.

Usually it celebrated nervous, mental and motor agitation, manifested excessive fussiness, agitated speech, increased responses to various stimuli (hyperreflexia).

The degree of functional disorders of organs and tissues, metabolic disorders, their specific biological significance are different depending on the variety of shock and its severity. Specificity of states of shock is detected, as a rule, only at the initial stage of its development. Later, with the growth of the degree and scale of life disorders, leading pathogenetic importance triad of interrelated and co-occurring pathogens: hemodynamic instability, hypoxia, and Toxemia.

Hemodynamic link

Violation of hemodynamics at shock is the result of disorders of the heart, change the tone of resistive and capacitive vessels, reducing BCC, changes in blood viscosity, as well as the activity of the hemostatic system factors.

1. Disorders of cardiac activity.

Causes:

- Direct action on the heart of extreme factors (mechanical trauma, toxins, severe hypoxia, an electric current, etc.).
- Hypercatecholaminemia cardiotoxic effects, high blood hormones of the adrenal cortex and thyroid.

Implication:

- A significant tachycardia.
- Various cardiac arrhythmias.
- Reduction of shock and cardiac output.
- Violations of the central organ, tissue and microcirculation.
- Systemic venous congestion.
- Slowing of blood flow in the microvasculature, most pronounced in the venules.

2. Change the tone of resistive and capacitive vessels.

Under the influence of shock factors of vascular tone at the beginning, tends to increase. The main reason - increased activity of the sympathetic-adrenal system and a significant increase in connection with the level of catecholamines in the blood. For some time, increased tone of the walls of resistance vessels (arterioles) helps to maintain systemic blood pressure.

The consequences of increasing the tone of the capacitance vessels walls (venules) - Increased blood flow to the heart.

- Increased blood supply, stroke volume, and as a consequence - perfusion pressure.
- Later (due to metabolic changes in tissues and organs) accumulate BAS lowering the tone of the vessel walls (both resistive and capacitive). These substances include adenosine, biogenic amines histamine, N0, PGE, I2.
- Under the influence of extreme factors (especially calling plasma - or blood loss) there is a redistribution of blood flow.

Manifestations of blood flow redistribution:

- Increase in blood flow (or at least no loss) in the arteries of the heart and brain.
- Simultaneous decrease in blood flow in the vessels of the skin, muscles, abdominal organs, kidneys (due to vasoconstriction). This phenomenon is called blood centralization.

Causes of blood flow redistribution:

- Uneven adrenoceptor content in different vascular regions. The highest number found in the walls of the vessel muscles, skin, abdominal, kidney and considerably smaller - in the heart and brain blood vessels.
- Formation of a large amount of myocardial tissue and cerebral vasodilating agents - adenosine, prostacyclin, NO, etc.

The value of blood flow redistribution:

- Adaptive. Blood supply to the heart and brain in the conditions of the phenomenon of centralization of blood circulation helps to maintain the life of the organism as a whole. On the contrary, these organs ischemia significantly exacerbates the shock.
- Pathogenic. Hypoperfusion vessels in the skin, muscles, abdominal organs and kidneys leads to the development in them of ischemia, the current slowdown in the microvasculature (especially postcapillaries and venules), disruption of fluid reabsorption in the venules. The latter causes a decrease in VCB and blood clots.

3. Reduction of the VCB, the change in blood viscosity and activity of the hemostatic system factors are identified at an early stage of shock states.

Implication:

- Increased blood viscosity.
- Reducing its strength.
- Formation of blood clots in the vessels of the microcirculation.
- Improving the content and / or activity of blood coagulation factors. The latter is mainly due to the damaging effect of shock factors agent hypercatecholaminemia, the release of Ca2 + from the damaged cells, and other factors.

Together, disorders of cardiac activity, tone of vascular walls, increasing their permeability and impaired reabsorption of fluid in the bloodstream is initiated by the growing violation of central and regional circulation and microcirculation for all varieties of shock.

The hypoxic link

The hypoxic link of pathogenesis is a major component of the pathogenesis of regular and shock.

Causes:

- Initially, hypoxia is usually the result of hemodynamic disorders and circulatory character wears.
- As the worsening state of hypoxia becomes mixed. This is the result of progressive respiratory disorders, changes in blood and tissue metabolic system.

Effects:

- Reduced the effectiveness of biological oxidation potentiates the disruption of tissues and organs, as well as the metabolism in them.
- Hypoxia is one of the reasons for the suppression of the activity of the antioxidant defense system of factors tissues. In this regard, they generated an excess of reactive oxygen species, lipid peroxidation reactions are activated and accumulate products of these reactions - peroxide, hydroperoxide, etc. and aldehydes.

Toxemic link

Toxemic link activated at an early stage of the shock.

Causes:

- The action of extreme factors (in toxic, toxic and infectious diseases, burns, and other types of anaphylactic shock).
- Damage to the extreme factors of cells and release of these large amounts of unclaimed BAS (kinins, biogenic amines, adenine and adenosine nucleotide, enzymes), normal and disturbed metabolism products, ions, denatured compounds.
- Violation of the inactivation and / or excretion of toxic compounds by the liver, kidneys and other organs and tissues.

Effects:

Increase intoxication potentiates hypoxia, hemodynamic instability, the functions of organs and tissues.

Metabolic link

Causes:

- Excessive activation of neural and humoral effects on tissues and organs,
- Upset hemodynamics in tissues and organs,
- Hypoxia,
- Toxemia.

Effects:

In general, changes in metabolism are characterized by a predominance of catabolic processes.

1. Protein content of the tissue, usually reduced. Simultaneously increasing their level of degradation products.

Reason - significant activation of proteolytic enzymes, under the influence of excess catecholamines, Ca2 +, H +, and other enzymes.

2. The total protein content in the blood is also reduced.

One of the leading causes of: output of low molecular weight protein fractions of blood vessels due to the significant increase in the permeability of their walls.

3. The level of glycogen in tissues is reduced. Causes:

- Glicogenmobilisation effects of excess catecholamines, glucocorticoid and other hormones;
- Inhibition of glycogen synthesis in the cells due to insulin deficiency;
- A consequence of these processes is hyperglycemia,

4. The residual (non-protein) typically nitrogen in the blood increases.

Causes:

- Activation of gluconeogenesis process;
- Disruption of the liver;
- A decrease of urea excretion by the kidneys,

5. Lipid metabolism is characterized by:

- Intensification of lipolysis in tissues;
- Increase in the content of free fatty acids, which are intensively oxidized, esterified, and subjected to lipid peroxidation;
- A decrease in the level of phospholipids in tissues, indicating the activation of phospholipase;
- Decreasing blood free fatty acids, because they are included in tissue metabolism rapidly (assuming sufficient for this level of ATP in the cells) and transformed into a free radical reactions. 6. Contents of adenine nucleotides (ATP, ADP, AMP) and inorganic phosphate in tissue varies in different ways.
- ATP level therein is reduced as a result of intensive ATP hydrolysis.
- Phosphate concentration drops because of their access to the blood.
- ADP and AMP content in the tissues increases as the ATP hydrolysis increased, and its resynthesis insufficient in oxygen deficit conditions.

7. The level of ions and fluid in tissues as a whole increases.

The reason - cytolemma damage, as well as the membranes of mitochondria and sarcoplasmic reticulum.

Manifestation - increase in the tissues [K +], [Ca2 +], [Na +], osmotic and oncotic pressure and fluid volume.

Aggravation of the above-described complex disorders of the functions of organs and tissues, metabolism and plastic processes in them, as well as the growing depletion of adaptive responses create the conditions for the transition stage adaptation (compensation) in decompensated shock.

Torpid stage

Stage of decompensation (deadaptation, progressive, irreversible, torpid) - as a result of the action of extreme factors and progressive failure of tissue functions, organs, systems, as well as the depletion of the body's adaptive capabilities.

In contrast to the compensation stage, the degree and extent of disorders much more pronounced. Various lesions develop simultaneously and potentiate each other. The most frequently observed decompensation functions of the kidneys, lungs, liver (syndromes "shock kidney", "shock lung", etc.). Under these conditions, organ failure function is extreme. This can cause the patient's death.

Neuroendocrine link

Consciousness at decompensation stage is not lost. However, in severe shock during signs of lethargy and confusion. This is manifested by the fact that the patient is delayed and often inappropriately answers questions, hardly versed in the environment.

The intensity of the effects of nerve and hormone levels:

- A reduced or retained at a higher level;
- The effects of neural and hormonal influences progressively reduced until absence. Causes:
- Significant damage to the nervous and other tissues.
- Significant physical and chemical changes in the tissues (acidosis, ion imbalance, hyperhydration, and others.).
- Reduced sensitivity (hyposensitization) cells to hormones and neurotransmitters.
- The fall of the severity of conditioned and unconditioned reflexes (hyporeflexia).
- Reduction in blood hormone levels of most endocrine glands.

The totality of these changes leads to an imbalance of neurotransmitters and as the content of hormones in the blood plasma and interstitial fluid and their effects. This is the reason for the disintegration and physical functional systems of the organism that causes discoordination and tends to minimize the functions of organs and tissues.

Hemodynamic link

At the stage of decompensation, hemodynamic shock pathogenesis link becomes crucial. Causes

- The progressive cardiac dysfunction, the development of his lack of contractile activity and arrhythmias.
- The total decrease in the tone of resistive and capacitive vessels. This eliminates the phenomenon of adaptive circulatory centralization. Systolic blood pressure in severe shock during reduced to 60-40 mm Hg, which is fraught with the termination of the filtration process in the kidney glomeruli and development of uremia.
- Further reduction bcc and increase in blood viscosity due to a yield of the liquid portion of blood into the extracellular space.

Manifestations

- Total hypoperfusion of organs and tissues,
- A substantial disorder of microcirculation,
- Capillarotrophic failure.

Changes in the vessels microvasculature:

- Slowing of blood circulation;
- The appearance in some regions vascular large number of so-called plasma capillaries (in which no blood cells), while others - the capillaries filled with blood cells or aggregates with signs phenomenon sludge and stasis.

Changes hemostatic imbalances are in the development of concentration and / or activity of coagulation factors, anticoagulative and fibrinolytic systems.

Effects

The development at the stage of decompensation of shock:

- DIC,
- Tissue ischemia,
- Degenerative changes in organs and tissues,
- Tissue necrosis,
- Hemorrhage therein.

The hypoxic link

Causes:

- Systemic disorders of hemodynamics,
- Hypoventilation lungs.
- Reduction of the VCB.
- Impaired renal function
- Disorders of metabolism.

- The development of severe hypoxia mixed type.
- Uncompensated acidosis.

Under such conditions, exacerbated metabolism disorders, impaired metabolic products accumulate more and more suppressed function of organs and tissues.

Toxemic link

Toxemia is characterized by:

1. The increase of blood and other biological fluids impaired metabolic products and physiologically active substances (e.g. lactic and pyruvic acids, fatty acids, polypeptides, biogenic amines);
2. accumulation of blood in the compounds:
   - Released from damaged and disrupted cells (enzyme, denatured proteins, ions, and various other impurities.);
   - Formed in the body due to failure of the liver and kidneys indoles, phenols, skatole, urea, uric acid and others.

These substances are contributing significantly to organ damage.

Metabolic link

Metabolic unit shock on decompensation stage appears:

- Dominated processes catabolism of proteins, lipids, carbohydrates, complex compounds (PL, glycoproteins, phospholipids, etc.);
- Minimization of intensity and metabolic processes in cells of the plastic;
- Overhydration cells;
- Accumulation of biological fluids unoxidized substances (lactic acid, pyruvic acid, CT et al.);
- An increase in tissue levels of lipid peroxidation products.

Cell link

Cellular link of the pathogenesis of shock on decompensation stage is characterized by:

- Increasing suppression of the activity of enzymes and cell activity;
- Damage and destruction of cell membranes;
- Violations of cell-cell interactions.

In general, lack of functions of organs and tissue hypoxia, toxemia, gross metabolic disorders cause significant deviations from normal vital parameters of homeostasis, manifested:

- Hypotension and collapse;
- A significant reduction in rates of pO2 and pH;
- An increase in the osmolarity of blood plasma;
- Increasing oppression of life of the organism as a whole.

PATHOGENESIS CERTAIN SHOCK

Features of different types of shock are mainly determined by their cause and nature of the response to her body. Given these two factors, below is a description of the individual and clinically relevant variants of shock.

Anaphylactic shock

It is a shock that occurs as the pronounced manifestation of anaphylaxis or atopy. Drug anaphylaxis occurs in 1 out of every 2700 hospitalized patients; 0.4-2 deaths per 1,000,000 per year from anaphylactic shock in response to a sting of Hymenoptera.

Etiology.

1. Medicines: antibiotics (especially penicillin) protein preparations (enzymes - trypsin, chymotrypsin; hormones - insulin, ACTH), and vitamin B1, NSAIDs, local anesthetics, drugs used for immunotherapy (allergen antiserum immunoglobulins vaccines).
2. The venom of stinging insects (bees, wasps, hornets).
3. Food products (fish, shellfish, cow's milk, eggs, beans, peanuts).
4. Contact with latex products (gloves, catheters).
5. Patients with cold urticaria at the general supercooling (eg, bathing in cold water) may develop anaphylactic shock Clinic.
6. Sometimes, anaphylaxis can occur for no apparent reason. Episodes are repeated, accompanied by an increase in histamine concentration in blood plasma. In such cases we say about idiopathic anaphylaxis.
7. Genetic predisposition (hypersensitivity to specific antigens).

Risk factors.

The presence of atopic diseases and anaphylactic reactions in the anamnesis.

Pathogenesis

1. The release of histamine with IgE - mediated degranulation of mast cells leads to the expansion of peripheral blood vessels (especially the arterioles), lower peripheral resistance, blood Escrow on the periphery due to increased peripheral vascular and blood pressure fall.
2. Unlike anaphylactic, anaphylactoid reactions occur under the influence of non-immune activators mast cells, such as iodinated X-ray contrast agents, the solutions of dextrans, and polymyxin, tubocurarine, opiates, thiopental, pentamidine, hydralazine, doxorubicin stilbamidina et al.

Manifestations

1. Arterial hypotension, syncope, shock. The interval between the appearance of symptoms of shock and exposure to allergens varies from a few seconds when the allergen injections or insect bite up to 15-30 minutes with ingestion of the allergen.
2. Nausea, vomiting, involuntary urination and / or defecation.
3. Itching, redness, possible urticaria, angioneurotic edema (skin, subcutaneous tissue, mucous membranes) allergic origin.
4. bronchial obstruction.
5. Spastic syndrome.
6. shortness of nasal breathing.
7. Difficulty swallowing (the first sign of laryngeal edema).
8. Expansion of the pupils.
9. Tachycardia.

Treatment. Careful monitoring of vital signs nA throughout the treatment period, and a few hours after relief of anaphylactic shock clinical symptoms may recur within 24 hours

- Principles: increased peripheral vascular resistance, recovery bcc, normalization of AAR and maintenance functions of vital organs. Emergency treatment: epinephrine, diphenhydramine, cimetidine (H2-receptor blocker), glucocorticoids.

Complications: recurrence of anaphylactic shock, shock kidney, liver shock, shock lung.

The course and prognosis: a favorable prognosis with timely emergency care; outlook deteriorates significantly when administered epinephrine later than 30 minutes after the first signs of anaphylaxis.

Toxico-infection- shock

Infectious-toxic shock syndrome - toxic shock in infectious diseases caused by exposure to high doses of the body of toxins and pathogens (or) the decay products of damaged tissues. Develop hypotension, oliguria, tachycardia, tachypnea, fever, microcirculation disorders due to diffuse cell and tissue damage by toxins. The main lesions are caused by endotoxin (thermostable lipopolisahiridny component of the cell walls of microorganisms). Less toxins are the cause of Gram-positive bacteria, viruses and yeasts.

Treatment:

1. Causal treatment

- Antibiotics (preferably appointment bacteriostatic drugs as microbicides, drugs can cause deterioration of the patient due to the rise of endotoxemia).
- Introduction antistaphylococcal plasma and γ-globulin (with a staph infection) or fresh frozen plasma (when unidentified exciter)

2. Pathogenetic therapy.

- Elimination of hypovolemia introduction volume dependent solutions.
- Improve the microcirculation introduction reopolyglucin.
- To maintain vascular tone - dopamine.
- For removal of intoxication - hemodes.
- If necessary - diuretics.
- Cardiac glycosides - indicated.

Cardiogenic shock

Cardiogenic shock - a shock with a sharp decrease in cardiac output and a decrease in oxygen supply of tissues as a result of violations of myocardial (heart attack, hemodynamically significant arrhythmias, dilated cardiomyopathy) or morphological disorders (acute valvular insufficiency, ventricular septal rupture, the critical aortic stenosis, hypertrophic cardiomyopathy). Cardiogenic shock hemodynamically characterized by an increase in end-diastolic left ventricular pressure (pulmonary artery wedge pressure> 18 mm Hg) reduction in cardiac output (cardiac index <2 L / min / m2), an increase in systemic vascular resistance decrease in mean arterial pressure (<60 mm Hg).

Compensatory mechanisms: ADH secretion, release of aldosterone and renin secretion of catecholamines.

Physiological reactions: decreased urine output, leading to fluid overload; vasoconstriction. causing an increase in afterload;

Pathogenesis. In addition to violations of myocardial contractile function, developed in the cardiogenic shock matters pain factor (myocardial infarction and pulmonary embolism). Depending on the pathogenesis and clinical features distinguish the following forms of cardiogenic shock:

- Reflex cardiogenic shock. A crucial role is played by disorders of vascular tone caused by reflex reactions.

- True cardiogenic shock due mainly to impairment of myocardial contractility.
- Arrhythmic shock associated with the occurrence of arrhythmia heart rate.
- Unresponsiveness shock. The term is used in relation to cardiogenic shock, not amenable to drug therapy.

Manifestations. The sharp drop in blood pressure on the background of signs of a myocardial infarction, acute myocarditis, etc. Adynamic Patients complain of severe weakness. Appearance: pointy facial features, pale, cyanotic skin, sticky cold sweat. Breathing palpitations, superficial. Pulse frequent, sometimes arrhythmic, weak filling. An important symptom - oliguria or anuria. In severe cardiogenic shock - loss of consciousness, joining pulmonary edema.

Treatment. Carry out the treatment of the underlying disease causing the cardiogenic shock, including surgery (drainage of pericardial tamponade, pulmonary embolectomy of the arteries, coronary bypass surgery, etc.).

Forecast. Mortality rate - more than 70%.

Burn shock

The cause of burn shock: extensive skin burns (usually more than 25% of its total surface) II and / or III degree. In children and the elderly develop shock occurs at a burn for about 10% of the surface of the skin.

The pathogenesis and manifestations

The main links of the mechanism of burns and traumatic shock similar.

Burn shock leads to:

- Frequent infections and sepsis burn surface development
- Severe toxemia
- Short-term erectile stage for heavy torpid
- Severe pain afferent impulses from the affected zone
- Part of the development of "shock kidney"
- Significant dehydration

Much pain afferent impulses from the burnt skin and soft tissues, which cause a generalized activation of the nervous and endocrine systems.

This leads to the development of a strong emotional, motor and speech excitement, activate the functions of organs and tissues, as well as materials in their metabolism.

The relatively short stage of compensation. Often it goes into decompensation stage before rendering the first medical aid.

The short first stage due to overexertion and the rapid depletion of adaptive reactions of the organism, as well as significant hemodynamic disorders and intoxication.

Severe dehydration resulting from massive loss of blood plasma. The latter is defined by a significant increase in the permeability of the vessel walls, especially in the area of the burn.

Increased blood viscosity, the development of the phenomenon of sludge, thrombosis and microcirculation disorders that develop as a result of a large loss of blood plasma.

Severe intoxication:

- Products of thermal denaturation of the protein, and proteolysis;
- BAS excess produced during tissue injury (kinins, biogenic amines, oligo and polypeptides, and others.);

Frequent damage to the kidneys caused by the violation of their blood supply and hemolysis of red blood cells.

Allergic reactions and diseases of the immune autoaggression. Observed in patients withdrawn from the state of shock and in the development of their burn disease. This is due to the denaturation of blood proteins and tissues as well as infection of the organism. Immunological reactions are contributing significantly to the severity of a burn shock and burn patients.

Septic shock

Septic shock is possible in case of peritonitis, infections of the urinary and biliary tract, pneumonia, necrotizing pancreatitis, septic abortion and childbirth. Most often, septic shock results from gram-negative bacterial action (E. coli, Klebsiella, Proteus), but may be pathogens, and other agents (gram-positive bacteria, viruses, fungi, protozoa).

Synonyms

- Toxic-infectious shock
- Endotoxin shock
- bacteremic shock
- Infectious-toxic shock

Traumatic shock

The reason traumatic shock: massive damage to organs, soft tissue and bone under the influence of mechanical factors (e.g., breakage or crushing of tissues and organs, the gap limb bone fracture and others.). Typically, mechanical injury combined with greater or lesser degrees of wound infection and blood loss.

The pathogenesis and manifestations

Traumatic shock is characterized by significant pain afferentation.

1. Stage of compensation.

Phase compensation for intensity and duration, typically correlates with the scale and the degree of injury: the greater, the shorter this stage, and vice versa. This is explained by the breakdown process of compensatory, protective and reduction reactions.

The patient is excited. Many spoke about the incident with it, tossing in bed, sensitive to touch or attempt to move it, and a lot of random gestures (hyperreflexia).

There have been signs of activation of the sympathetic-adrenal system.

- Pale skin and visible mucous.
- Expansion of the pupils.
- Increased blood pressure, increased heart rate, blood flow velocity.
- The increase in respiratory rate.

These reactions have a definite adaptive value: in terms of damage the body, especially in the presence of blood loss, they are an important component of the general adaptation syndrome and process emergency hypoxia compensation.

Record the increased release of steroid hormones by the adrenal glands. It promotes the use of glucose nervous tissue, myocardium and other organs, as well as the stabilization of blood vessels and cell membranes. The latter prevents excessive increase their permeability and correspondingly reduces the swelling of tissue, degree of thickening of the blood, out of the lysosomes and further from the cells into the extracellular fluid enzymes and other macromolecular compounds, ie, It reduces the level of toxemia.

2. Stage of decompensation.

Stage of decompensation is characterized by:

- Depletion and the breakdown of adaptive reactions of the organism;
- Progressive reduction in the efficiency of neuroendocrine regulation;
- increase failure of organs and their systems.

- Fall in blood pressure and the development of a collapse (systolic blood pressure can be reduced with mild shock and 90 mm Hg, with an average - up to 70 mm Hg, with a heavy - up to 40-50 mm Hg).
- Increased heart rate (up to 180-210 per minute), its weak content, loss of its individual waves (a sign of cardiac arrhythmias).
- Increased massive exit of fluid from the vascular tissue.
- Reduction of the bcc (below the norm by 25-40% or more) and an increase in Ht.

- Blood hypercoagulability and thrombosis, especially in the microvasculature. Later may develop disseminated intravascular coagulation, thrombosis, fibrinolysis, and hemorrhage.

- The deposit of a large amount of blood in the vessels of the abdominal cavity, lungs, spleen, liver. This leads to a progressive decrease in cardiac output, blood pressure.
- Impaired microcirculation in lung edema them, obstruction of the bronchioles and focal atelectasis, which causes acute respiratory failure. These changes are known as the syndrome of "shock lung."
- A significant reduction in the blood supply to the kidneys, thrombosis and sludge, edema and ischemia parenchyma, form cylinders in the kidney tubules. It causes acute renal failure and uremia ("shock kidney").
- Significant disorders of hemodynamics in the liver. This leads to the development of its total insufficiency (a syndrome of "shock liver").
- Disorder hemodynamics in blood vessels of the mesentery and the walls of the intestine, causing a violation of the digestive tract function with the development of auto-infection and intestinal auto-intoxication.

These and other disorders (without effective medical care) potentiate each other can lead to inhibition of the body's vital functions and death.

Bacteremic shock

Bacteremic shock - toxic shock with bacteremia caused by hitting into the blood large dose of bacterial toxins. Painful shock - shock caused by strong pain stimulation (eg, trauma). Hemolytic shock - a shock that occurs when intense hemolysis (for example, during a transfusion of incompatible blood).

Hemorrhagic shock

Hemorrhagic shock - a kind of hypovolemic shock. There are mild hypovolemic shock (loss of 20% VCB), moderate (20-40% loss VCB), severe (loss of more than 40% of VCB). Compensatory mechanisms: the secretion of antidiuretic hormone, aldosterone, renin, catecholamines. Physiological reactions: decreased urine output, vasoconstriction, and tachycardia.

Pathogenesis. The adaptation of the patient to the blood loss is largely determined by changes in the capacity of the venous system (containing a healthy person up to 75% of blood volume). However, the ability to mobilize blood from the depot limited to: the loss of more than 10% of VCB begins to decrease central venous pressure, and decreased venous return to the heart. There is a small release syndrome, leading to a decrease in the perfusion of tissues and organs. In response, there are non-specific compensatory endocrine changes. The release of ACTH, ADH and aldosterone leads to delay kidney sodium, chloride and water while increasing potassium loss, and a decrease in urine output. The result of the release of epinephrine and norepinephrine - peripheral vasoconstriction. From the blood off less important organs (skin, muscle, gut), and stored blood supply to vital organs (brain, heart, lungs), ie there is centralization of circulation. Vasoconstriction leads to profound tissue hypoxia and acidosis development. Under these conditions, the proteolytic enzymes of pancreas enter the blood and stimulate the formation of kinin. Recent increased vascular permeability that facilitates transfer of electrolytes and water in the interstitial space. As a result, in the capillaries occurs aggregation of red blood cells, creating a base for the formation of blood clots. This process immediately precedes irreversible shock.
Manifestations. With the development of hemorrhagic shock distinguish 3 stages.

1. Compensated reversible hemorrhagic shock. The volume of blood loss does not exceed 25% (700-1300 ml). Tachycardia moderate AP or not modified or slightly lowered. Desolation

subcutaneous veins, decreased central venous pressure. There is a sign of peripheral vasoconstriction: cold extremities. The amount of urine is reduced by half (at a rate of 1-1.2 ml / min).

2. Decompensated reversible hemorrhagic shock. The volume of blood loss of 25-45% (1300-1800 ml). The pulse rate reaches 120-140 per minute. Systolic blood pressure decreased below 100 mm Hg, pulse pressure decreases the value. There is a severe shortness of breath, partly offset by

metabolic acidosis respiratory alkalosis, but also able to be a sign of shock lung. Boosts cold extremities, acrocyanosis. It appears cold sweat. The rate of urine - less than 20 ml / h.

3. The irreversible hemorrhagic shock. Its appearance is dependent on the duration of circulatory decompensation (typically hypotension over 12 hours). The volume of blood loss greater than 50% (2000-2500 ml). Pulse exceeds 140 minutes, systolic blood pressure drops below 60 mmHg or not is determined. Consciousness is absent. Develops oligoanuria.

Treatment. In hemorrhagic shock absolutely contraindicated vasopressor drugs (epinephrine, norepinephrine) because they exacerbate peripheral vasoconstriction). For the treatment of arterial hypotension, which developed as a result of blood loss, consistently perform the procedures listed below.

1. Catheterization of the main vein (usually in the subclavian or internal jugular).

2. The jet or drip intravenous blood substitutes (polyglucin, gelatinol, reopolyglucin etc.). Determine the blood group of the patient and its compatibility with the donor blood. Perform blood transfusion.

Fresh frozen plasma transfusions, and if possible - or albumin protein. The total volume of fluid for intensive therapy can be calculated as follows.

- If blood loss of 10-12% of the bcc (500-700 ml) the total amount of liquid should be 100-200% of the volume of blood loss at a ratio of salt and plasma expander solutions - 1: 1.
- With an average blood loss (up to 15-20% of VCB, 1000-1400 mL) compensation in the amount of produce 200-250% blood loss. Transfusion of blood medium consists of (in amount 40% blood loss) and salt and colloidal solutions in the ratio 1: 1.
- When a large blood loss (20-40% of VCB, 1500-2000 mL) total volume transfused liquid is not less than 300% of blood loss. Blood poured into a volume of 70% of the lost. The ratio of salt and colloids - 1: 2.
- If massive blood loss, constituting 50-60% of VCB (2500-3000 mL), the total volume of infusion should be at 300% higher than the loss of blood, with transfused blood volume should be at least 100% of blood loss. Saline solutions and colloids are used in a ratio of 1: 3.

3. Combating metabolic acidosis: infusion of 150-300 ml of 4% sodium bicarbonate solution.
4. Glucocorticoids simultaneously with the start of blood substitution.
5. Removing spasm of peripheral vessels.
6. Inhalation moistened oxygen.
7. Hyperthermia - natural cooling (ice encasing it bubbles), analgin (2 ml of 50% solution) or reopirin (5 ml) deep V / m.
8. Broad-spectrum antibiotics.
9. Maintaining diuresis (50-60 ml / h). 10. Cardiac glycosides.

Transfusion shock

Transfusion shock - a shock that occurs when incompatible blood transfusion as an extreme expression of post-transfusion reactions. Hypovolemic shock - a shock that occurs when the loss of more than 20% of BCC because of the acute bleeding or dehydration.

Obstructive shock

Obstructive shock occurs when a massive pulmonary embolism, cardiac tamponade, atrial myxoma, acute valvular stenosis (eg, prosthetic valve thrombosis) or tense pneumothorax; cardiac output falls sharply due to the reduction of blood flow obstruction or ventricular filling with adequate bcc, myocardial contractility, and vascular tone.

Pleurapulmonary shock

Pleurapulmonary shock - traumatic shock arising in case of damage (including during surgery) in the chest and thoracic cavity due to over-stimulation of the receptors of the visceral and parietal pleura.

Spinal shock

Spinal shock - a temporary sharp drop in excitability of nerve centers located below the level of spinal cord injury, manifested by the weakening of the corresponding spinal reflexes. Toxic shock - a shock caused by the impact on the body of toxic products of tissue decay or bacterial toxins (eg, traumatic toxicosis, bacteremia).

SHOCK TREATMENT

The effectiveness of the treatment of states of shock is largely determined by the time intervals at which it started after exposure to the causative agent: the shorter the interval, the more successful the treatment and prognosis.

Etiotropic treatment

Etiotropic treatment is carried out by eliminating or mitigating the shock genicity factors:

- The impact of the termination of the damaging agent,
- The use of anesthesia and / or local anesthetics.

These measures are aimed at preventing and / or reducing the severity of excessive pathogenic afferentation from pain and other extero-, intero- and proprioceptors. In the treatment of shock, timely and effective causal treatment largely determines the success of the treatment of the victim.

Pathogenetic treatment is aimed well as the stimulation of adaptive therapy).

Pathogenetic therapy

at breaking the key elements of the mechanism of shock, as reactions and processes (the latter known as sanogenetic

1. Elimination of disorders of the central, organ, tissue and microcirculation. It is achieved by a complex of measures.

With all the varieties of shock (but especially in traumatic and burn) decreased VCB, disturbed blood supply to organs and tissues, as well as the blood flow in the vessels of the microvasculature. In order to eliminate or reduce the degree of these variations:

- Patients poured blood, plasma and / or plasma substitutes (the latter including high-colloids, preventing fluid into the extravascular output channel);
- Simultaneously (or in the above liquids) use so-called buffer solutions (sodium hydrogencarbonate, etc.), Potassium chloride normalization acid-base balance and liquids containing various ions to remove them imbalance;
- Used vasoactive drugs and cardiotropic allowing normalize myocardial contractile function, vascular tone and eliminate heart failure;
- Use tools that reduce the permeability of the vessel walls: calcium drugs and corticosteroids.

2. The elimination or reduction of the degree of disorder of blood supply to organs and tissues. As a rule, it can reduce the severity of disease functions of most organs and tissues.

3. Eliminating (or reducing the degree) failure of external breathing. Enabled by means of the ventilator, breathing gas mixtures with increased oxygen content, the use of respiratory analeptic.
4. Improve the blood supply of the kidneys, and in severe cases - the use of the apparatus "artificial kidney" (if there is evidence of renal failure and uremia development).
5. Removal of hypoxia, acid-base balance deviations and ionic balance. It achieved typically by normalizing the circulatory, respiratory, function kidney and other organs. However, along with this conduct and special events: breathing gas mixtures with increased oxygen, hyperbaric oxygenation, the introduction of anti-oxidants.

6. Reduction of toxemia. For this purpose, conduct special medical action:
- Hemosorption and plasmapheresis;
- The introduction of antidotes and antivenoms;
- Infusion of colloidal solutions (absorbent toxins), blood, plasma, plasma expanders, diuretics.

e elimination of toxemia in substantially contributes to the normalization of the kidneys, liver, gastrointestinal tract.

Symptomatic therapy

Symptomatic treatment is aimed at reducing the painful and unpleasant sensations, feelings of fear, worry and anxiety, usually accompanied by shock. For this purpose, cardiotropic and vasoactive substances, a respiratory analeptic, various psychotropic drugs (antipsychotic, tranquilizers, antidepressants, sedatives, stimulants, etc.).

Coma

Coma occurring in various pathological processes can be divided into the following groups.

1. Conditional primary CNS (neurogenic). This group includes anyone that is developing at a stroke, traumatic brain injury, epilepsy, inflammation and tumors of the brain and its membranes.

2. Developing for violations of gas exchange.
- Hypoxic. Connected with insufficient intake of oxygen from the outside (suffocation) or impaired transport of oxygen in severe acute circulatory disorders and anemia.
- Respiratory. Due to hypoxia, hypercapnia, and acidosis due to significant violations of pulmonary gas exchange in respiratory failure.

3. The conditioned metabolic disorders with insufficient or excessive production of hormones (diabetic, hypothyroid, hypocorticoid, hypopituitary coma), an overdose of hormonal preparations (thyrotoxic, hypoglycemic coma).

4. Toxogenic coma associated with endogenous intoxication during poisoning, kidney failure and liver (hepatic, uremic coma), pancreatitis, or with exposure to exogenous poisons (coma for poisoning, including alcohol, organophosphorous compound, etc.).

5. Primarily due to loss of water, electrolytes and energy substances (hyponatremic coma at a syndrome of inappropriate ADH production, chlorhydropenic that develops in patients with persistent vomiting, alimentary-dystrophic, or hungry, coma).

Disturbances of consciousness

Comatose states are characterized, above all, a violation of consciousness.

The degree of disturbance of consciousness often plays a decisive role in the outcome of many diseases and pathological processes. Therefore, to determine the state of consciousness - one of the highlights when the patient survey, especially in emergency situations.
The main types of disorders of consciousness.

Disorders of consciousness are usually subdivided into a change of consciousness and the consciousness of oppression.

1. Changes in consciousness - productive forms of impaired consciousness, developing on the background of wakefulness. They are characterized by a disorder of mental functions,

perverted perception of the environment and the self, is not usually accompanied by immobility. These include delirium, amentia and twilight disorders of consciousness. They are the leading symptoms of most mental disorders and treated in psychiatry.

2. Depression of consciousness - non-productive forms of disturbance of consciousness, characterized by deficiency of mental activity with a reduction in the level of consciousness, a distinct inhibition of intellectual functions and motor activity.

To determine the degree of depression of consciousness worked well so-called Glasgow scale (Scottish scale). Assessment of the degree of oppression of consciousness produced in points. For example, if 8 points above the patient has a good chance of improvement; less than 8 - life-threatening situation; 3-5 - very likely death (especially if detected fixed pupils).

Classification

To assess the level of consciousness use the following classification.

1. Clear consciousness.

2. Obnubilation - limited waking state; usually associated with sleepiness: - Moderate (I),
- Profound (II).

3. Sopor - areactivity condition from which the patient can only be removed for a short time with intensive re-stimulation.

4. Coma - areactivity condition from which the patient can not be deduced by the stimulation, even primitive protective reflexes may be absent during a deep coma:
- Moderate (I), - Deep (II),
- Prohibitive (III).

Disorders of consciousness can be short or long, with light or deep. Transient loss of consciousness observed in syncope, whereas epileptic seizures, it may take a little longer, and at the brain injury - sometimes several hours. Prolonged loss of consciousness usually occurs in severe intracranial lesions, or metabolic disorders.

Types of violations of consciousness

1. Stunning is the result of an increase (by the action of pathogenic factor) excitability threshold. In connection with this stunning characterized by decreased sensitivity to external stimuli.

Implication:

With stunning notes:

- Preservation of consciousness against the background of varying degrees of violations of sequence, logic and clarity of thinking (confusion).
- Physical inactivity.
- Disorientation in situation.
- Increased drowsiness (somnolence). Strong stimuli (sound, light, pain) only temporarily withdrawn from the patient's state of stunned.

Status stun often preceded by stupor.

2. Sopor condition characterized by general inhibition of psychic activity, significant inhibition of consciousness (but not its complete loss unlike coma), loss of voluntary movements, while maintaining reflexes (unlike coma) on strong sound, light and painful stimuli. The latter is usually expressed transient motor responses, moan, movement of facial muscles.

Often considered stupor stage of coma, loss of consciousness prior (ie, the actual development of the coma).

3. Delirium is characterized by:
- False affective perception of the environment and events, its own role in them (delusions);

- Spontaneous endogenous visual and / or auditory sensations (hallucinations);
- Verbal and motor excitation.

In a state of delirium the patient is actively involved in the events they perceived (he can attack, defend, escape, and clearly describe "visible" images of them, "leads a conversation" with an absent interlocutor).

4. Amentia characterized by:

- Incoherence (disrupted character) thinking;
- Violation of orientation, perception of surrounding objects, events, and self;
- Chaotic, disorderly excitation;
- Unfocused physical activity.
- In case of recovery the patient does not remember (amnesia) of what happened to him during amentia.

5. Twilight state of consciousness characterized by:

- Violation of orientation in the environment;
- Detachment from the place of real events;
- Behavior based on hallucinations (usually intimidating character);

udden onset and termination;

- Often committing aggressive acts.
- Episode amnesic twilight state.

6. Stupor

From the different types of violations and loss of consciousness must be distinguished stupor. When stupor consciousness is not lost. Stupor - a condition characterized by complete immobility, the weakening or lack of reaction to external sound, light and pain stimuli on the background of the saved consciousness.

Stupor often develops in patients with mental health (eg, schizophrenia), as well as with severe somatic (eg, in patients with severe malabsorption syndrome) disease. Stupor is also observed in a number of depressive states (for example, after the loss of a loved one) and strong psychogenic traumas, developing under the influence of various extreme factors.

CAUSES OF COMA

This causes a variety of factors. They are usually divided into exogenous and endogenous.

The latter can be infectious and noninfectious.

Exogenous factors

Exogenous factors - pathogenic environmental agents, usually of great strength, toxicity and / or destructive nature.

- Various traumatic (usually brain) factors (electricity, mechanical trauma to the head).
- Thermal treatment (hyperthermia, heatstroke, hypothermia).
- Significant changes in barometric pressure (hypo - and hyperbaric).
- Neurotrophic toxins (alcohol and its surrogates, ethylene glycol, toxic doses of drugs, sedatives, barbiturates, etc.).
- Infectious agents (neurotropic viruses, botulinum and tetanus toxins, pathogens of malaria, typhoid, cholera).
- Exogenous hypoxia and anoxia.
- Radiation energy (large doses of ionizing radiation).

Endogenous factors

Endogenous factors leading to the development of the coma, the result of severe disorders of vital activity. They observed an unfavorable course of various diseases and disease states. These conditions lead to significant deviations from normal vital parameters and constants, excess or deficiency of metabolic substrates and / or oxygen in the body.

- Pathological processes in the brain (ischemic stroke, tumor, abscess, swelling, etc.).
- Lack of blood circulation (cerebral hypoxia).
- Respiratory failure (the brain during hypoxia status asthmaticus, asphyxia, pulmonary edema).
- Pathology of the blood system (massive hemolysis, severe anemia).
- Endocrinopathies (hypoinsulinism, hypo - and hyperthyroid condition, adrenal insufficiency).
- Hepatic insufficiency, disorders of the digestive system (malabsorption syndrome, intestinal autointoxication, and / or self-infection).
- Kidney failure.
- Comatose states are developing in a number of cases in severe progressive course of collapse and shock.

GENERAL PATHOGENESIS AND MANIFESTATIONS Pathogenesis comatose states, regardless of their causes, including some key links.

Hypoxia, a violation of processes of power supply cells, intoxication, acid-base balance disorder, an imbalance of ions and fluid disturbances electrogenesis imbalance content blockers and their ffects are developed in all organs and tissues.

However, the greatest extent they are expressed in the brain. That is why the obligatory sign of the coma is a loss of consciousness. Damage to other tissues and organs, severe disorders of the neuroendocrine regulation of their functions, are responsible for the progression of multiple organ failure and increasing the oppression of life of the organism as a whole.

Common manifestations of comatose states

Organs and systems	altered function
Nervous and Endocrine	Disorders of consciousness, loss of consciousness, hypo - and arephlexia imbalance BAS and their effects
Cardio-vascular system	Heart failure, arrhythmias, hypotension and collapse, blood flow redistribution, capillarotrophic failure
Lungs	respiratory insufficiency
blood system and hemostasis	Deposition of blood, changes in blood viscosity syndrome trombohemorragic
Liver	Liver failure
kidneys	kidney failure
Digestion	Lack of cavity and membrane digestion, intestinal autointoxication, autoinfection

Hypoxia and violations of the processes of power supply

Upset oxygen supply to tissues and organs is the cause or coma, or its pathogenetic link.

Violation observed with substrate causes cell failure ensure biooxidation therein.

1. ATP Resynthesis in brain neurons is provided mainly due to the oxidation of glucose energy in the reactions of tissue respiration. Neurons in the brain that are the norm in most oxygen-structures under conditions of hypoxia are the most vulnerable object in the body.

- In the brain mass is about 2% of body weight, accounting for about 20% of the cardiac output of blood. However, the brain (and heart) no stocks of ATP. In this connection, the termination (or decrease) in the oxygen delivery to the brain and / or metabolic substrates precludes its normal functioning.

- Termination of the cerebral circulation after 8-10 to lead to critical shortages of oxygen and energy supply disturbances neurons. The result is a loss of consciousness.
- Comes within the next 4-7 minutes depletion of glucose, as well as suppression (due to the increasing acidosis) anaerobic metabolism accompanied by irreparable expenditure of ATP energy. In this regard, the activity is inhibited by specific neurons lost consciousness and begin to develop rapidly progressive degenerative processes.
- Disintegration in neurons large molecular organic compounds, as well as excess accumulation in Na + and other ions leads to a significant increase in intracellular osmotic and oncotic pressure. This in turn leads to overhydration nerve cells, combined with the fluid outlet of the container in the interstitium (ie, brain edema), venous hyperemia and hemorrhage in the brain substance.
- Even while maintaining cerebral blood flow at the level of about 20% of normal develop delirium, stupor or coma.
- Brain Neurons are damaged to a greater extent in ischemia than hypoxemia. With normal perfusion pressure vessels in the brain, even at lower paO2 to 30 mmHg and below, no signs of neuronal necrosis.
- Damage to cells in a coma is aggravated due to the disorder of transport processes ATP energy from the places of their production in the mitochondria (in the process of tissue respiration) and cytosol (during glycolysis).
- Violation of the energy supply of cells, ultimately, causes their dysfunction, degeneration and the development of the disorder plastic processes in them. To the greatest extent this is expressed in the brain and heart. In this regard, in patients who are in a coma, lost consciousness, reduced severity or absent reflexes; develop arrhythmia and contractile function of the heart failure and hypotension; disturbed frequency and operation frequency of the neurons of the respiratory center, decreases the amnt of alveolar ventilation, which leads to worsening of respiratory insufficiency and hypoxia.

Intoxication

Coma of any origin characterized by the accumulation in the body of toxic substances. They enter the body from outside (at coma exogenous origin) and formed in himself (with endogenous coma). A number of comatose states cause neurotropic toxins, alcohol and its surrogates, ethylene glycol, fungal toxins; Drugs when used incorrectly (for example, narcotics, barbiturates, tranquilizers).

- Toxic substances and their metabolic products have the most pathogenic effect on the neurons of the stem and the cerebral hemispheres of the brain, endocrine glands, heart, liver, kidneys, blood cells. Toxins damage the membrane structure of cells and enzymes. In connection with this function is inhibited neuronal cortical and subcortical structures. This in turn leads to disorders of the cardiovascular, respiratory, endocrine and digestive system, kidneys, liver, blood systems, hemostasis, and others.
- Intoxication metabolic products aggravates the violation of the liver detoxification and excretory activity of the kidneys. Thus, when a diabetic coma significantly increased blood levels of CT, lactic and pyruvic acids. Thus, for example, an excess of acetoacetic acid substantially inhibits the activity of brain neurons and autonomic ganglia.
- When hepatic coma blood levels of putrescine, cadaverine, phenol derivatives significantly increased, indole, skatole (formed during the decay of the large intestine of protein) and ammonium compounds (carbon dioxide and ammonium carbamate, ammonium hydroxide). Normally these compounds are inactivated at the liver and excreted from the body by the kidneys. However, the liver and / or kidney failure called toxic compounds and their derivatives potentiate the damage to the brain and other organs, exacerbating the patient's condition.

Disorders acid-base balance

Deviation indicators acid-base balance - a natural phenomenon in a coma from any source.

1. In most cases, acidosis develops. Causes:

- Hypoxia circulatory, respiratory, hematic and tissue type.
- Impaired renal function (inhibition acid- and ammoniogenesis, reduced their excretory functions).
- Disorder of the liver (the suppression of the inactivation process, the CT). This increases the degree of acidosis.

2. Much less frequently and tend to temporarily registers the development of alkalosis (eg, during hyperventilation lungs or liver coma, accompanied by a significant increase in blood ammonium ions).

Imbalance ions and water

Violation of the content and the relationship between the individual ions in the cytosol, cell-cell and other biological fluids is an important part of the pathogenesis of coma, particularly when it heavy flow.

Manifestations

- Loss of K + cells.
- The development of hyperkalemia.
- Increase in the cells [H +].
- Increase Intracellular [Na +].
- Hyponatremia.

These changes are a consequence of decreased activity of Na +, K + - ATPase plasmolemma and damage cell membranes.

- Reduction of [Cl] and / or [HCO-3].
- Some versions of coma (eg, renal or hepatic) are characterized by different changes in the ionic balance. The above options are comatose states may be accompanied by an increase in blood levels of aldosterone (due to its increased synthesis in the adrenal glands or the reduction of inactivation in

e liver), which determines the reabsorption of Na + and K + excretion in the kidney tubules to the development of hypernatremia and hypokalemia, respectively.

- Hyperosmia - and hyperoncia. It is the result of hydrolysis large molecular compounds (LP, proteoglycans, glycogen and others) to molecules of small and medium-sized (proteins, amino acids, glucose, MC).

Effects

- Hyperhydration marrow and other organs (for diabetic hyperosmolar coma, in contrast, developed hypohydration cells potentiates their damage).
- Increased fluid content in the intercellular space.
- An increase in the volume of fluid in the bloodstream (hypervolemia).
- Swelling of the brain and lungs.
- Diarrhea, vomiting, polyuria (eg when hypocloremic, diabetic, hyperosmolar coma). They can cause progressive extracellular first, and then a total hydropenias.
- Significant increase in blood viscosity.
- Violation of organ and tissue and microcirculation.
- Disseminated aggregation of blood cells, it hypercoagulability and thrombosis (DIC).

Violations electrogenesis

Implication:

The breakdown process of power supply cells, damage to their membranes and enzymes naturally cause disturbances:

- The formation of membrane potential and action potential.
- Excitability (decrease, increase);
- Conduction of excitation. To the greatest extent it is manifested in the structures of the brain and heart.

Effects:

- Disturbances of consciousness, until his loss.
- Seizures.
- Disorders of the nervous centers (especially respiratory and cardiovasomotor).
- The development of cardiac arrhythmias, including ventricular fibrillation.

Imbalance BAS and their effects

Implication:

- Violation of the synthesis and release of biologically active substances of different classes of cells: neurotransmitters, hormones, cytokines, and others.
- Activation of disorder, inactivation, delivery of biologically active substances to the target cells.
- Disruption of interaction of BAS with their cellular receptors.
- Upset response of the target cells. This is caused by damage to cell membranes and intracellular mediators implementation hormone effects of mediators and cytokines.
- The collapse of the physiological and functional systems.
- Minimization of functions of organs and tissues, energy expense and plastic processes.
- The transition to the so-called metabolic regulation of the functions of organs and tissues. Usually it is preceded by the development of a terminal condition.

FEATURES PATHOGENESIS OF SOME COMATOSE

The specificity of certain types of coma is usually detected at an early stage of its development. At these stages occur more especially the causes of coma and of initial units of its pathogenesis. With increasing severity of comatose states reduced their specificity and increasingly manifest their common traits.

Traumatic coma

Cause: trauma, accompanied by severe cerebral concussion and loss of consciousness.

Unconsciousness in traumatic coma can last from several minutes to a day or more.

Manifestations

1. The motor responses and eye opening to painful stimulus is absent or greatly reduced.
2. It is absent or the patient emits inarticulate sounds.
3. Hypo - or areflexia.
4. Breathing and heart rate are violated.
5. BP and BCC reduced, even if there was no blood loss.
6. Frequent vomiting.
7. Involuntary urination.
8. In connection with the brain injury, focal hemorrhages and edema in his taped neuropathological symptoms: paralysis (usually hemiparesis), pathological reflexes, local sensitivity disorders, convulsions.
9. The liquor usually blood observed.
10. At the turn of the bones of the skull base there specific features:
    - Symptoms of damage to the nuclei of neurons VII and VIII pairs of cranial nerves;
    - In orbit bruising ("points" symptom);
    - Bleeding and outflow of cerebrospinal fluid from the ear passages, nose, mouth.

Apoplectic coma

Causes

- Bleeding in the brain.
- Acute local brain ischemia with the end result in a heart attack (thrombosis or embolism, major brain artery). The last condition is called stroke (due to the rapidly growing changes in the brain and the body's vital activity disorder).

Risk factors

- Hypertension (especially periods of hypertensive crises).
- Atherosclerotic changes in cerebral vessel walls.

- Ischemia and hypoxia of the brain (as a result of local or widespread disorders of blood circulation in it);
- A significant increase in the permeability of microvessels wall;
- Rapidly increasing swelling of the brain substance.
- For stroke characteristic of the secondary disorders of blood circulation around the ischemic brain region with a rapidly increasing signs of loss of sensation and movement.

Manifestations

1. Apoplectic coma due to a brain hemorrhage:

- The patient suddenly loses consciousness;
- His face (in typical cases) purple;
- Visible blood vessels dilated and pulsate noticeably;
- Pupils do not react to light;
- Tendon reflexes reduced or absent (hyporeflexia), there are pathological reflexes (Babinski et al.);
- In connection with the damage and irritation of the brain substance intensively growing respiratory distress (it is noisy, raucous);
- Violated swallowing;
- Marked hypertensive response and bradycardia.

2. When apoplectic coma as a result of ischemic stroke is usually observed: - Recurrent episodes of rapid passing of vertigo;
- Unsteady gait;
- Violations of speech; - Sensitivity disorders;

- Sometimes - syncope (these disorders are the result of transient disorders of blood circulation in the vessels of different brain regions with the development of its transient ischemia);
- Disorders of consciousness, until his loss;
- Hypotension;
- Bradycardia;
- Cardiac arrhythmias;
- A rare shallow breathing;
- Pale and cold skin, and mucous membranes;
- After prolonged ischemia (depending on the affected area of the brain) are identified: hyporeflexia, movement disorders, sensory disturbances.

The consequences of a brain hemorrhage or ischemic stroke. They are different and depend on:

- Scale and topography of lesions,
- The degree of hypoxia and brain edema,
- The amount of damage to homes,
- The severity of hypertension,

- Atherosclerosis severity,
- Age of the patient.

Apoplectic coma refers to the most unfavorable flowing coma, fraught with the death or disability of the patient.

Hypochloremic coma

Reason hypochloremic (chlorhydropenic, chloroprivic) coma - a significant loss of body chlorinated substances. This occurs when:

- Long-term repeated vomiting (in patients with endogenous intoxication, food poisoning, toxemia of pregnancy, pyloric stenosis, intestinal obstruction);
- Incorrect treatment with diuretics;
- A long salt-free diet;
- Renal failure on its polyuric stage;
- Fistulas of the small intestine.

Considering that at the above conditions relatively slowly lost Cl, Na + and K +, as well as compensate for the effects of adaptive mechanisms in the coma typically develops gradually.

Implication:

- Disturbances of MT and AP due to a decrease in blood plasma and other extracellular body fluids content Na +, K +, Cl- and other ions.
- Disorders of cell excitability.
- Violations of the specific and non-specific cell functions. As a result, develop: muscle weakness, lack of exercise, lethargy, rapid physical and mental fatigue, dizziness, and sometimes convulsions, constant thirst, hypohydration.

Due to the loss of body fluids:

- Skin and mucous membranes dry,
- Reduced tissue turgor,
- The facial features are sharp,
- Dry tongue,
- Develops oliguria,
- Ht significantly increased,
- BP is usually reduced,
- BCC reduced
- Ion imbalance,
- Circulatory disorders of the brain.

Brain Ischemia leads to growing frustration of consciousness: stunned state becomes psychomotor retardation and loss of consciousness ends.

Therapies coma

I. Etiotropic treatment is essential. It largely determines the prognosis of the patient. In this regard shall take measures to stop or mitigate the pathogenic action of the causal factors.

1. Traumatic coma:

- Eliminates the damaging factor,
- Used painkillers, local anesthetics,
- If necessary – narcosis

2. When a coma caused by intoxication of the organism used: - Specific antidotes,
- Antitoxins,
- Gastric lavage, - Diuretics,

3. When a diabetic coma:

- The calculated insulin dose is administered,
- If necessary, together with glucose solution (for the prevention of hypoglycemic coma).

4. When used antibacterials coma infectious origin (antibiotics, sulfonamides, and antiseptics, acting on the intestinal flora and urinary tract).

II. Pathogenetic therapy is key to the treatment of any patient in a coma.

It includes measures aimed at the blockade, the removal and / or weakening of the damaging effects of the basic pathogenesis of coma: hypoxia, intoxication, disorders acid-base balance, an imbalance of ions and fluid, BAS and their effects.

1. The anti-hypoxic therapy: - Mechanical ventilation.

- Breathing gas mixtures with increased oxygen content. - Hyperbaric oxygen therapy.

- Introduction of antioxidants (e.g., glutathione agents, selenium, SOD, catalase, and ubiquinone al.).

- Normalization of the heart and vascular tone.

2. The elimination or reduction of the degree of intoxication by:

- Blood transfusion, plasma, and plasma substitutes, physiological sodium chloride solution.

- The introduction of solutions containing organic compounds large molecular - polyglucin, reo polyglucin etc. These drugs combined with diuretics to stimulate excretion of body fluids and being of toxic substances;

- In severe cases, as well as in renal insufficiency, uremic coma - hemodialysis and peritoneal dialysis.

3. Normalization of indicators AAR, the balance of ions and fluid by:

- Controlled administration of a buffer solution with the necessary (for each patient is chosen individually to the laboratory data into account) the content and ratio of various ions;

- Blood transfusion, plasma, plasma substitutes.

4. Normalization of BAS and their effects. Used for this purpose:

- Adrenal hormones (glucocorticoid and mineralocorticoid, androgenic steroids, catecholamines); - The pancreatic hormones (insulin, glucagon);

- Neurotransmitters (acetylcholine, norepinephrine), and others.

These preparations normalize the function of the heart, kidney, brain and other organs homeostasis indicators, activate the adaptive specific and nonspecific reactions.

III. Symptomatic therapy is aimed at optimizing the functions of organs and systems, the elimination of seizures, pain, painful sensations in the pre- and post coma periods. Used for this purpose:

- Anticonvulsants;

- Analgesic agents (including drugs); - Cardiotropic and vasoactive drugs;

- A respiratory analeptic.

Given that the coma is characterized by severe disorders of functions of organs, systems, regulatory mechanisms of the body, the effectiveness of therapeutic interventions should be monitored permanent registration status of the vital functions (cardiac, respiratory, renal excretory function, etc.). Consciousness, and homeostasis parameters.

Allergy

Providing antigenic homogeneity and identity of the body is the main objective of the NBI system. Upon detection of foreign antigenic information carrier (virus, bacteria, parasites, tumor cells and other abnormal protein.) Immune system usually provides its neutralization, destruction and removal from the body. Immune reactions do not always occur at this scheme. Often, in simultaneously implementing them are damaged and destroyed its own cells and non-cellular structures. This is accompanied by the disorder of functions of many tissues, organs and physiological systems. This type of immune response is called an altered reactions abnormally

increased sensitivity (hypersensitivity). Austrian pathologist background Pirque in 1906 coined the term "allergy" to describe these reactions.

Allergies - is an immune response that occurs when re-exposed to an antigen (allergen), and is accompanied by damage to its own tissues, the development of inflammation and / or dysfunction of individual organs and systems.

Allergy - a pathological form of the immunogenic reactivity. Formed, usually as a result of re-exposure of cells of the immune system to a foreign antigen. It is accompanied by a change (usually

- increase) the sensitivity to a given antigen. Characterized detection, and often the destruction and elimination of foreign antigen, as well as damage to the body's own structures, reduced its adaptive capacity and impaired his life.

Common allergy symptoms

An allergy is an abnormal form of immune reactivity. In contrast to its physiological form - immunity, allergic reactions characterized by, among others, four of obligatory feature.

1. Damage, along with the alien, the body's own structures.
2. Inadequate response to an antigen:
- In the words: usually hyperergic response (hypersensitivity reaction).
- In scale: usually generalization reactions or a tendency to it.
3. Development, besides the allergic reaction and other - in the body of non-immune disorders.
4. Reduction of the adaptive capacity of the organism as a whole.

If allergic reactions are often achieved and biologically useful result. He is to detect, localize (fixation), destruction and removal from the body causes allergies - antigen. In some cases (for example, after the relief of anaphylactic shock, spontaneously or as a result of treatment), the body becomes immune to the shocked antigen. In other words, when the allergic, like at a normal immune response, achieves the same goal - to maintain the homogeneity of antigenic individuality and body by removing foreign bodies from it.

Prevalence

1. An allergy is diagnosed in 10-20% of the population. The most common among allergic diseases occur pollinosis (allergic reactions to pollen, grass, trees and flowers), bronchial asthma, contact allergy, anaphylactic reactions.

2. The incidence of various forms of allergy is increasing progressively: allergic diseases concede only lead to cardiovascular, cancer and infectious diseases. To a large extent this is caused by a wide, often unfounded, the application of medicines, household chemicals, vaccination, use of low-quality cosmetics, synthetics, pesticides and herbicides.

CAUSES OF ALLERGIES

The allergen - the substance that causes the allergic reactions.

Allergens are called antigens that trigger allergic reactions (immune reaction with tissue damage own). Allergens have all the properties of antigens.

The hapten (incomplete antigen) initiating immune responses only after the connection with body tissue proteins. In this form conjugated (complex) antigens that are sensitized body.

For haptens micromolecular compounds include: drugs, simple chemicals (bromine, iodine, chromium, nickel, etc.), Products of nonprotein nature (some microbial products, polysaccharides and others.).

Classification and characterization of allergens

On the origin and nature:

I. Exogenous allergens (exoallergen):

Non-Infectious nature:

1. Nutritional (nutritional). It is believed that the food - it is not only a source of replenishment of energy and plastic materials, and allergic and toxic aggression factors.
2. Drugs. The uncontrolled and often unreasonably extensive use of drugs (especially antibiotics, vaccines) resulted in sensitization (hypersensitivity) of millions of people, the development of allergic diseases and complications, ranging from pruritus, urticaria and ending fatal anaphylactic shock.
3. Pollen. The pollen of many plants, which is usually a complex of proteins with carbohydrates or pigments pollen, causes allergic disease - pollynos characterized by a primary lesion of the respiratory tract and mucous membranes of the eyes.
4. Dust. The so-called household dust is a complex composition. It includes the residues of organic compounds of animal, plant, microbial origin, synthetic fabrics, plastics and other chemicals, as well as inorganic compounds. One of the most active of the active principles are house dust mites.

Production dust gets antigenicity due to bacterial and fungal infections especially, as well as impurities of pesticides, herbicides, minerals, insects and other particles. The dust causes allergic defeat predominantly respiratory.

5. Epidermal (horny skin flakes, bird feathers, animal fur particles, etc.).
6. Household chemicals (various dyes, detergents, creams, cosmetics, deodorants, and so on.).
7. Serum (human and animal blood products containing the antibody. They are often used for the diagnosis, treatment and prevention of different diseases).
8. Physical factors (high or low temperature, radiation of different wavelengths, and others.).

Infectious and parasitic (saprophytic and pathogenic microorganisms, viruses, fungi, parasites, etc.).

II. Endogenous allergens (endoallergen).

These include cell components (proteins, polypeptides, large molecular polysaccharides, lipopolysaccharides) and tissue own organism acquiring allergenic properties due to: the action of physical, chemical, and other infectious exogenous origin agents, leading to the formation of denatured protein complexes of proteins with exogenous allergens (haptens), which can perform the role of lipids, nucleic acids, many drugs; damage cells that become targets for the immune system (for example, cells in which the hapten is fixed).

On Waterways penetration allergens into the body:

1. Respiratory. These penetrate through pollen, dust, aerosols, epidermal allergens, some drugs, etc.
2. Nutritional. Food allergens cause allergic diseases are not only the digestive system, but also breath (allergic rhinitis, bronchial asthma), of the skin and mucous membranes (urticaria, allergic eczema, etc.).
3. "Contact". Through the skin and mucous membranes of low molecular weight substances can penetrate, topically applied drugs (e.g., ointments containing antibiotics), dyes, wood resins, creams, etc.
4. Parenteral (blood serum, drugs, poisons insects - bees, mosquitoes, etc.).
5. Transplacentally (some drugs, such as antibiotics, protein preparations, etc.).

Terms of allergic reactions

The important conditions for the development of an allergic reaction is allergen properties and features of reactivity.

1. The properties of the allergen (as generally antigen) is determined by its molecular weight, chemical heterogeneity, genetic foreignness, dose contact paths in the body, etc.

2. The state of reactivity largely determines the possibility of allergies, especially its current (form, prevalence, intensity) and outcomes. Are important individual genetic predisposition to allergic reactions. It is significantly higher in people who were in the pedigree of a person suffering from some form of allergy.

Types of allergies

There are several classifications of allergies, which are based on different criteria. The most reasonable, meaningful and informative are the criteria based on the features of the pathogenesis of hypersensitivity reactions (Gell and Coombs classification), the nature of the allergens, the origins of allergenic antibodies or sensitized lymphocytes and the development of clinical manifestations of time after exposure to resolving agent.

Hypersensitivity types

Widely adopted by Gell and Coombs classification of hypersensitivity subdivides into four main types (depending on participating in the mechanisms for their implementation). Many immunopathological processes are mediated by a combination of several of hypersensitivity reactions.

Nature sensitizing and allowing allergens

1. Specific allergy. In most cases of clinically significant allergic reaction is re-entering the body or entity in him the same allergen (called permissive), which at the first exposure sensitized the body (ie, caused the production of specific AT and T lymphocytes). This allergy is called specific.

2. Non-specific allergy. Often develop the so-called non-specific allergic reactions.

- Parallergy. When the protein allergens (such as sensitizing and permitting) have similar, but not identical structure, develop parallergic reaction (for example, during mass vaccinations against various diseases with small intervals of time between them).
- Heteroallergy. Another option is a non-specific allergy - heteroallergy. It arises when resolving agent is any antigenic effect - cooling, overheating, intoxication, irradiation of the organism, etc. An example could be the development heteroallergy diffuse glomerulonephritis or acute exacerbation of chronic intermittent after exposure to the patient of any of the above factors. Direct resolving agent in such cases is clearly not itself cooling, intoxication or radiation, and those substances (allergens) that are formed in the body under the influence of these factors.

Depending on the type of immune system cells, taking advantage of participation in the development of allergy, conventionally distinguished:

1. B-lymphocyte dependent ("humoral" immunoglobulin). The group of B-lymphocyte dependent include such forms of allergy in the mechanisms that play a leading role produced by B-lymphocytes circulating in body fluids humoral antibodies belonging to different classes of immunoglobulins. Depending on the types of Ig, other "partners" of the immune process and its effects distinguish several varieties of allergy. The most studied B-lymphocyte-dependent types of allergic reactions which can be realized with the participation of IgE, IgG, IgM. B lymphocyte dependent, hypersensitivity reactions immunoglobulin may be "moved" from sensibilized to another organism using serum containing the allergic antibody. This reproduction of allergy is called "passive transfer" it.

2. T lymphocyte dependent ("cell") allergic reactions. The group of T lymphocyte-dependent allergic reactions attributed, in the pathogenesis of which the leading role belongs to T-

lymphocytes and produced their physiologically active substances - lymphokines. The last act as intermediaries - mediators in the allergic mechanisms. The causes of these reactions may be foreign cells and tissue proteins, low molecular weight chemical compounds, including some medications used topically (e.g., antibiotics), microbial antigens. Allergy condition of this type may be "passively" healthy

ent transferred from sensitized lymphocytes or "extract" of such cells, e.g., blood transfusion or administration of drugs in serum.

Genesis allergenic AT or sensitized lymphocytes

1. Active allergy. In most cases, the allergic reaction is actively formed in the body, i.e. in response to the introduction or the formation in it of allergen in the body. This kind of allergy is called active.

2. Passive allergy. If the allergic reaction is the result of contact with blood or its components organism containing allergic AT (e.g., blood transfusion or blood plasma), any of the previously allergic lymphocytes of the organism, the reaction is called a passive moved transplanted.

Dates of clinical manifestations

Depending on the time of onset of clinical manifestations of allergy after exposure to the organism sensitized Ag allowing allergic reactions are divided into immediate, delayed and delayed.

1. The immediate type allergic reactions clinically manifested immediately or within a few minutes after exposure to the organism with an allergen (eg, allergic rhinitis, allergic conjunctivitis, anaphylactic shock, atopic form of bronchial asthma).

2. Allergic reactions delayed (late) of the type identified in a few hours (but usually within the first 5-6 hr.) After contact with the permissive antigen (e.g., hemolytic anemia, thrombocytopenia or leukopenia allergic genesis separate species serum sickness).

3. The delayed-type hypersensitivity is usually recorded in a few hours or days (usually 1-2 days) after exposure to the allergen allowing sensitized on the body (eg, tuberculin, brucellin test, syphilitic reactions, contact dermatitis).

The above criteria for the classification of allergic reactions, on the one hand, are not absolute (one and the same reaction may be characterized with different criteria products) and on the other hand, beyond these criteria are not stringent. So, if you characterize atopic form of bronchial asthma, according to the leading link of pathogenesis, it is a type I hypersensitivity reactions (by Coombs and Gell). However, in its pathogenesis links are specific to type III hypersensitivity reactions and IV; on the identity of the sensitizing allergen and allowing atopic form of bronchial asthma is a specific reaction, but some asthma attacks can occur and, after cooling (which is typical for heteroallergii); origin of sensitizing antibodies this form of asthma - active, although repeated blood transfusion recipient may appear in asthma attacks and under the influence of the same antigen that induced asthma donor (indicating a passive recipient genesis of asthma); at the start of a bronchial asthma attack, it usually refers to the immediate type allergic reactions, but some patients have delayed the beginning of the attack - after 60-80 minutes. Consequently, in actual clinical situations one or the other kind of an allergic reaction in an individual patient should be characterized by a maximum criteria and characteristics.

Stage allergic reactions

The dynamics of any allergic reactions can be divided into three sequentially developing stages: immunological, pathobiochemical and pathophysiological (clinical manifestations).

Immunological stage

Immunological stage (sensitization, primary contact) is to develop a more coherent and interrelated phenomena.

- Detection of allergen (antigen) immunocompetent cells.
- Processing of antigen by antigen presenting cells and the transmission of information about him or part of an antigen to the lymphocytes (presentation).
- Synthesis plasma cell pools Ig allergic and / or proliferation of sensitized lymphocytes.
- The formation of immune memory cells.

- Fixing Ig sensitized lymphocytes and preferably in the region of localization and upcoming sensitizing allergen allergic reaction (during the development of its local forms), or in biological fluids - blood, lymph, cerebrospinal fluid (in its generalized form).

Clinically, the condition of sensitization hardly manifested. It can last a few days, months or even years. However, it can detect the abnormality of reactive properties sensitized bodies, the activity of certain enzymes, concentration Ig, separate pools of immunocytes and other changes in the body.

To this purpose special allergy tests carried out, for example, by application to the skin intended allergen. If sensitization to these allergens in the area of its application on the skin develops a characteristic reaction (redness, swelling, accompanied by itching, pain and other symptoms). If it is impossible, or patient health hazards allergy tests performed using in vitro suspected allergen and a patient's blood or leukocytes.

Pathobiochemical stage

Pathobiochemical (biochemical reactions) during the second stage of developing ingested or education in it the same antigen, which it was sensitized. In this form complexes with specific allergen AT and / or sensitized lymphocytes. In a number of reactions in this complex and includes factors of the complement system.

- Immune complexes are recorded in the areas with the largest concentration of the allergen and the AT (at local allergic reactions, for example - Arthus phenomenon) or in biological fluids (in generalized allergy, for example - anaphylactic shock or serum sickness).
- Under the influence of these complexes are formed in different cells, are activated and released biologically active substances of different spectrum - mediators of allergy. Each type of allergic reaction to a set of other mediators of allergy.
- Mediators cause allergy as a further development of an allergic reaction (its dynamics, specificity, severity, duration), and the formation of distinctive and general and local signs. Under the action of immune complexes, mediators of allergy and secondary metabolites produced in the cells, tissues and organs - targets - developing specific to certain forms of allergic reactions, physico-chemical and functional changes.

Pathophysiological stage

Stage of clinical manifestations (allergic reactions, pathophysiological) is characterized by the development of a local pathological processes (in target cells and target tissues), and generalized disorders of vital activity.

- Pathological processes of local character. They consist in the development of various types of dystrophy, inflammation, increased permeability of vascular wall disorders regional circulation, capillarotrophic failure, hypoxia, microvascular thrombosis, edema of tissues.
- Disorders of life of the organism as a whole. Thus, in allergic bronchial asthma develop respiratory failure with allergic postinfarction myocardium (syndrome Dressler) - heart failure, diffuse glomerulonephritis - kidney failure, Hashimoto's thyroiditis - deficiency of thyroid hormones in allergic enterocolitis - malabsorption of food (malabsorption syndromes), etc.

Pathogenesis of allergic reactions

In 1964 Gell and Coombs proposed a classification, there are four types of hypersensitivity reactions, which are based on differences in the immunological mechanisms of clinical manifestations of hypersensitivity reactions. Belonging to one or another type is determined by the location and class of antibodies that interact with an antigen and subsequent activation of effector cells and tissue damage.

The first (I) Type - anaphylactic - type of immediate hypersensitivity reactions, or reaginic reaction - mediated AB IgE class. Interaction with the allergen fixed on the surface of mast cells or basophils, IgE-AT activation leads to the cells and is accompanied by the release of newly deposited mediators.

The second (II) type - cytotoxic. Formed IgG- or IgM-AT directed against antigens on the cells are an individual's own tissues. Binding of AT to the antigens on the cell surface leads to complement activation. The damaging effect of the membrane attack complex of complement attracted leukocytes. In addition, the process may involve cytotoxic T-lymphocytes with receptors for the Fc-IgG. By binding to IgG, they participate in the formation of AT-dependent cellular cytotoxicity.

Third (III) type - immunocomplex. This includes diseases of immune complexes formed when antigen complexes with IgG- and IgM-AT, having critical dimensions. Not removed from the bloodstream complexes are retained in the capillaries of the body tissues where they activate the complement system, causing the influx of leukocytes and activation of extracellular release of enzymes that damage the tissue in which the immune complex is fixed.

The fourth (IV) type of reaction - cell-mediated (T-cell-dependent) - delayed type hypersensitivity. Contact with the antigen of the antigen-specific receptors on Th1 cells leads to an increase in clonal populations of lymphocytes and their activation with release of inflammatory lymphokines.

Fifth (V) type (antireceptor) (for Roit). Type immune diabetes, immune thyroid disease, pituitary and may be one of the mechanisms of asthma, atopic dermatitis. Antibodies (IgG), circulating in the blood. Antigen (cell membrane receptors) fixed on the cell surface.

Type I allergic reactions

With the development of type I hypersensitivity reactions (immediate type reactions, atopic, reaginic, anaphylactic) interact with antigen AT (IgE), which leads to release of biologically active substances (mainly, histamine) from mast cells and basophils.

The cause allergic reactions type I most often exogenous agents (components of pollen, grasses, flowers, trees, animal and vegetable proteins, some medicines, organic and inorganic chemicals).

Examples of type I reactions - pollinosis, exogenous (acquired), asthma, anaphylactic shock.

The same type of reaction are pseudoallergy (including idiosyncrasy).

Pathogenesis.

Stage sensitization

In the initial stages of the interaction of antigen sensitization is carried out (the allergen) with immunocompetent cells as antigen processing and presentation form specific for the antigen Clone plasma cells which synthesize IgE and IgG (human apparently G4). These are fixed on the AT target cells of the first order (mainly mast cells) having a large number of high affinity receptors for them.

It is at this stage, the body becomes sensitized to that allergen.

Pathobiochemical stage

Repeated allergen enters the body it interacts with a fixed first order surface (mast cells and basophilic leucocytes) molecules target cells IgE, which is accompanied by an immediate release of granule contents of the cells into the extracellular space (degranulation). Degranulation of mast cells and basophils at least has two important consequences:

First, the internal environment falls wide variety of biologically active substances that have a variety of effects on different effector cells (especially contractile and secretory);

Secondly, many biologically active substances, in the released cell degranulation target first-order, second-order-activated target cells (neutrophils, eosinophils, lymphocytes, platelets, monocytes and macrophages), which in their turn are secreted by a variety of bioactive substances.

BAS, stand out from the target cells of the first and second orders, called mediators of allergy. With the participation of mediators of allergy done numerous stage effects, and the totality of which implements a reaction of hypersensitivity of type I.

Secretion of cell mediators of allergy and their implementation effects associated with:

- Increasing the permeability of the walls of microvessels and the development of tissue edema,
- Circulatory disorders,
- Luminal narrowing of the bronchial tubes, bowel spasm,
- Mucus hypersecretion,
- Direct damage to cells and non-cellular structures.

The main groups of mediators of allergic type I reactions and their effects

Chemotactic effect:	Improving the tone of smooth-muscle cells:
ECF NCF TNF leukotriene B4 kinins	histamine, serotonin Leukotrienes B4, C4, D4, nrF2a, D4 thromboxane kinins
Increased vascular permeability:	Regulation of cell-cell interactions:
histamine serotonin PGF2a leukotrienes C4, D4	TNF, IL (1, 2, 3, 4, 5, 6) GM-CSF y-IFN chemokines
Changing the tone of vascular walls:	The cytotoxic / cytolytic effect:
adenosine histamine serotonin Pg E2, I2, D2, kinins	hydrolase, arilsulphatase TNF reactive oxygen species free radicals lipoperoxide connection

Note. ECF - eosinophil chemotactic factor, NCF - neutrophil chemotactic factor, GM-CSF - granulocyte colony-stimulating factor and macrophage.

Stage Clinical manifestations

A certain combination of the above and other effects, and creates the uniqueness of the individual clinical forms of allergy. The most common mechanism for the described developing pollen allergy, allergic forms of asthma, allergic conjunctivitis, dermatitis, gastroenterocolitis and anaphylactic shock.

Pseudoallergic reaction

Similar to the above described changes in pathobiochemical type I allergic reactions observed in the so-called pseudoallergic reactions. Recently developed after enteral or parenteral ingestion of various agents: foods (chocolate, egg white, fish, milk and citrus fruits, some fruits etc.), Drugs, herbicides, pesticides, etc. One of such forms of pathological hypersensitivity (often. inherited a predisposition) to certain food and drugs received a special name, "idiosyncrasy".

An important feature of pseudoallergic reactions is their development with no apparent period of sensitization. It is also important that they are often detected in patients with total or hepatic insufficiency (undergoing viral hepatitis, malaria, chronically exposed hepatotropic poisons) or selectively impaired liver function by inactivation of biogenic amines (eg, histamine) and other vasoactive substances.

The rapid and significant increase in the content of these substances in the blood after introduction into the body and leads to the manifestation of pseudoallergic reactions, urticaria, rash of various types, local pruritus, erythema, angioneurotic edema, diarrhea, asthma attacks, and even states, resembling anaphylactic shock.

Allergic reactions type II

hen hypersensitivity reactions of type II AB (usually IgG or IgM) bound to antigen on the cell surface. This leads to phagocytosis, activation of NK cells or complement mediated cell lysis

system. Clinical examples include the destruction of blood (immune cytopenia), lungs and kidney lesions at Goodpasture syndrome, acute transplant rejection, hemolytic disease of the newborn.

The prototype of the type II allergy is a cytotoxic (cytolytic) reactions of the immune system, aimed at the destruction of certain foreign cells - bacterial, fungal, tumor, virus-infected transplanted. However, unlike these, allergic reactions of type II, firstly, the body's own cells are damaged; Second, due to the formation of excess cytotropic mediators of allergy is often damage to the cells becomes generalized.

Causes

Cause allergic type II reactions are most often the chemicals with relatively low molecular weight (including drugs containing gold, zinc, nickel, copper, and sulfonamides, antibiotics, antihypertensives), and hydrolytic enzymes in an excess accumulating in the extracellular fluid (for example, lysosomal enzymes or microorganism cells with their massive destruction) and reactive oxygen species, free radicals, of organic peroxide, and inorganic substances.

These (and quite possibly other) agents are responsible for one common result - they alter the antigenic profile of individual cells and non-cellular structures. This produces two categories of allergens.

1. Altered cell membrane protein components (blood cells, kidney, liver, heart, brain, spleen, etc. and endocrine glands.).
2. The modified acellular antigenic structures (e.g., liver, myelin, kidney glomerular basement membrane, collagen, etc.). Involvement in allergic reactions of non-cellular structures is often accompanied by damage and lysis of neighboring cells.

Normally, the immune system secures the destruction and elimination of these unit and have become antigenically alien structures by type of magic bullet. The development of an allergic reaction, this process makes large-scale, leading to damage to a large number of cells. In addition,

the picture is aggravated due to the natural development of inflammation in the area of allergic reactions and the appearance of damaged cells during inflammation.

Stage sensitization

1. Switched antigens transformed B lymphocytes into plasma cells synthesizing IgG subclasses 1, 2 and 3, and IgM. These classes AB can communicate with components of complement.

2. Ig specifically interact with altered antigenic determinants on the surface of cells and non-cellular structures of the body. Thus complement realized - and antibody immune cytotoxicity and cytolytic mechanisms:

- Complement the destruction of membrane antigens of foreign cells.
- Antibody cell damage and lysis of the foreign antigen carrier.

As can be seen in allergic reactions of the type II is not only neutralized by foreign antigens, but also damaged and lysed (especially with the participation of complement-reactions) own cells and non-cellular structure.

Pathobiochemical stage

1. Complement reaction. The cytotoxicity and cytolysis implemented by Break cytolemma target cells and its opsonization.

- Violation of the integrity of the membrane of the target cell is achieved through activation of the action of the complex "AB + AG" complement system.

The sequential activation of complement components leads to a relatively slow S5678 damage the cell membrane, S56789 - faster. Even more effective in complex S3b56789. These complexes are called membrane attack. As a result, the pores formed cytolemma 5-20 mm in diameter. Through them, the cell receives passively Na +, Ca2 + and other ions. In this connection rapidly and significantly increased intracellular osmotic pressure. Cage hyperhydratation, cytolemma hypertension and it breaks - comes "osmotic explosion" of the target cell.

- Cytolysis carried through opsonization of target cells by complement factors, as well as IgG and IgM. In this case, under the influence of a complex of antigen and activated AT mainly (but not exclusively) S4b2a3b factors. Their presence stimulates adhesion to target cell phagocyte release of these enzymes and their subsequent activation of lysosomal generation of reactive oxygen species, free radicals and other agents that lyse antigenically heterologous cell.
- Similarly, the structure can be damaged and non-cellular basement membranes, which is fixed to a foreign antigen. The activated components of the complement system, located in the body fluids - blood, interstitial fluid, and others, can enhance damage scale, impacting not only on the antigenically alien structure, but also on cells and non-cellular entity not having such antigen Furthermore, generalization of damage is achieved due to alterations in the enzymes the body structure of lysosomes, reactive oxygen species, free radicals are released from phagocytes and other cells in the area of allergic reactions.

2. The antibody-dependent cellular cytolysis is carried out without the direct involvement of complement factors.

- The direct cytotoxic effect and have cytolytic cells having the killer effect: macrophages, monocytes, granulocytes (mainly neutrophils), natural killer cells, T-killer cells. These cells are sensitized antigens. Killer action they carry out by contact with IgG in the Fc fragment-AT. Thus FaB-IgG is reacted with a fragment of the antigenic determinant on the target cell.
- Cytolytic effect of killer cells is realized by the secretion of hydrolytic enzymes, the generation of reactive oxygen species and free radicals. These agents reach the surface of target cells are lysed and the damage it.

- Along with antigenically altered cells during reactions can be damaged and normal cells. This is due to the fact that cytolytic agents (enzymes and other free radicals.) Is "injected" sighting a target cell and secreted into the extracellular fluid killer near it, and the other where the - unmodified cells antigenically. The latter is one of the characteristics that distinguish this type of allergic reaction, the immune - the impact of cytolysis.
- Mediators of allergic reactions of the type II.

Main groups of mediators of allergic reactions of type II and their effects.

1. Damage and perforation of the cell membrane:

- A complex of factors of the complement system (membrane attack complex): S5678 (slow action), S56789 (more rapid effects) S3b56789 (fast effective action);
-active oxygen species;
- Free radicals are organic or inorganic substances;
- Peroxides substances (mainly lipids);
- Enzymes killer T cells, damaged and destroyed cells.

2. Activation of phagocytosis:

- C3b complement factors, C3a, C5a, S4b2a3b complex;
- Lipid hydroperoxides.

Stage Clinical manifestations

The above-described cytotoxic and cytolytic reactions are the basis of the formation of a number of clinical syndromes of allergic nature: the so-called "medicinal" cytopenias (erythrocyte, leukocyte, thrombocytopenia); agranulocytosis; allergic or infectious and allergic forms of nephritis, myocarditis, encephalitis, hepatitis, thyroiditis, polyneuritis and others.

Allergic reactions type III

For hypersensitivity reactions type III (immunocomplex, precipitin) characterized by the formation of immune complexes. Complexes formed by the antigen and the corresponding AB, activate the complement system, resulting in the development of inflammatory response. Clinical examples: serum sickness (after the introduction of foreign proteins or medication), extrinsic allergic alveolitis, lupus and glomerulonephritis after infection.

The cause of allergic reactions of this type are well soluble proteins re-enter the body (for example, by injection of serum or plasma, vaccination bites some insects inhaled substances containing proteins, infection by microbes, fungi) or formed in the body (for example, in the development of infections, trypanosomiasis, helminthiasis, tumor growth, paraproteinemia and others.).

Stage sensitization

1. B cells produce and secrete IgG and IgM, having a pronounced ability to form precipitates when exposed to antigen. These precipitates are called immune complexes and disease pathogenesis in which they play an essential role immunocomplex.

- If the immune complexes formed in the blood or lymph, and then recorded in the various tissues and organs, the developing systemic (generalized) form of allergy. An example of it can serve as serum sickness.

- In cases where immune complexes formed vessels and is fixed in certain tissues, local develop allergies (e.g., membranous glomerulonephritis, vasculitis, periarteritis, alveolitis, Arthus phenomenon).

- The most frequently recorded immune complexes in the walls of the microvessels on kidney glomeruli basement membrane, in the subcutaneous tissue on myocardial cells, in the synovial membranes and articular fluid.

- Local allergic reactions of type III are always accompanied by the development of inflammation.

2. High levels of IgG and IgM precipitating detected 5-7 days after the appearance of the antigen in the body. 10-14 th day, due to tissue damage under the influence of immune complexes and the development of acute inflammation, clinical signs of disease appear.

Pathobiochemical stage

In connection with the fixation of immune complexes in tissues, as well as the activation of the reactions for their removal in the blood and tissues appear allergy mediators, which (according to their effects) can be grouped into several groups.

Main groups of mediators of allergic reactions of type III and their effects

1. Damage to cells and non-cellular structures:
- Membrane attack complexes S5678, S56789, SZ56789
- Enzymes of phagocytes and destroyed cells
- Reactive oxygen species and free radicals

2. Induction of an inflammatory response in the area of allergy: - Factors damage cells and non-cellular structures
- Stimulators of phagocytosis - Chemotactic factors
- TNF
- Kinins;
- Leukotriene B4
- Complement factors C3a, C3b, C5a (anaphylatoxin), C4b2a3b, C5, S5b67

3. Increased permeability of vessel walls and basement membranes:
- Histamine, serotonin
- Leukotrienes C4, D4
- Complement factors C3a, C5a activation of thrombosis:
- Factor XII (Hageman)
- thromboxane

Implementation effects of these bioactive substances leads to cell damage and non-cellular structures. This causes the development of acute inflammation with its characteristic of local and general signs.

Removing immune complexes with the participation of granulocyte and mononuclear cells accompanied by the release of a number of other biologically active substances (leukotrienes, Pg, chemoattractant, vasoactive agents, procoagulant and others). It potentiates and broadens the scope and degree of allergic tissue alteration, as well as developing in connection with the inflammation.

Increasing the permeability of the vessel walls leading to tissue edema and immune complexes promotes penetration of small and medium size blood into tissues, including - a wall of the vessels themselves to the development of vasculitis.

Increased permeability and loosening of basement membranes (e.g., kidney cells) provides penetration and fixation of immune complexes in them.

Proagregantov activation and procoagulant creates conditions for thrombus formation, microcirculation disorders, ischemic tissue development in their degeneration and necrosis (for example, the phenomenon of Arthus).

Stage Clinical manifestations

Direct effect of immune complexes on the cells and tissues and secondary reactions that develop in this connection, the implementation effects of mediators of allergy and reactivity characteristics in individual patients lead to the development of different clinical versions type III allergy. This type of allergic reaction is a key component of the pathogenesis of serum sickness, membranous glomerulonephritis, alveolitis, vasculitis, periarteritis nodosa, the phenomenon of Arthus and others.

Type IV allergic reactions

In Type IV hypersensitivity reactions (cell-mediated, delayed-type) not participating AT, and T-cells, interacting with the respective antigen (sensitized T cells) that attract macrophages into the hearth of allergic inflammation. The sensitized T cells after antigen binding have any direct cytotoxic effect on target cells or their cytotoxic effect is mediated via lymphokines. Examples of reactions of the type IV - allergic contact dermatitis, tuberculin skin test for tuberculosis and leprosy, and transplant rejection reactions.

Causes

- The components of micro-organisms (pathogens of tuberculosis, leprosy, brucellosis, pneumococci, streptococci), single and multicellular parasites, fungi, helminths, viruses and virus-containing cells.
- In-house, but modified (eg, collagen) and foreign proteins (including those located in vaccines for parenteral administration).
- Haptens example, drugs (penicillin, procaine), small molecule organic compounds (dinitrohlorfenol).

Stage sensitization

- There is a differentiation antigen-T cells, namely CD4 + helper T 2 (T-effector delayed hypersensitivity reactions) and CD8 + cytotoxic T lymphocytes (killer T cells). These sensitized T cells circulate in the internal environment of the body, performing a supervisory function. Part of lymphocytes is in the body for many years, keeping the memory of the antigen.
- Repeated exposure of immune cells to the antigen (allergen) causes blast transformation, proliferation and maturation of many different T-lymphocytes, but preferably T-killers. They exhibit together with phagocytes and subjected to degradation foreign antigen, and - the bearer.

Pathobiochemical stage

Sensitized T-killer cells destroy foreign antigens structure directly acting on it.

T-killer cells and mononuclear cells to form and secrete in the area of allergic reaction mediators of allergy, regulatory functions of lymphocytes and phagocytes, as well as suppress the activity and destroy target cells.

At the outbreak of allergic reactions of type IV is a series of significant changes.

- Damage, destruction and elimination of target cells (infected by viruses, bacteria, fungi, protozoa, etc.).
- Alteration, destruction and elimination of unmodified cells and non-cellular tissue components. This is because the effects of many alternating BAS antigen non-dependenr (non-specific) and apply to normal cells.
- The development of the inflammatory response. At the outbreak of allergic inflammation accumulate predominantly mononuclear cells: lymph - and monocytes, and macrophages.

Frequently, these and other cells (granulocytes, mast) accumulate around the small veins and venules, forming perivascular cuffs.

- The formation of granulomas consisting of lymphocytes, mononuclear phagocytes, which are formed from them epithelioid and giant cells, fibroblasts and fibrous structures. Granulomas typical of type IV allergic reactions. This type of inflammation is referred to as granulomatous (in particular with tuberculin, brutsellinovyh and similar reactions).
- Microhemo- disorders or developmental lymphocirculation capillarotrophic failure, tissue degeneration and necrosis.

Stage Clinical manifestations

Clinically, the above changes are manifested in different ways. The most common reactions are manifested as an infectious-allergic (tuberculin, brucellosis, salmonellas), in the form of diffuse glomerulonephritis (infectious and allergic genesis), contact allergies - dermatitis, conjunctivitis.

Testing of immediate type hypersensitivity.

Testing in vivo:

- Diagnostic provocative allergen skin tests: Applicator sample:
- Epidermal - the imposition of an allergen; in the case of a positive reaction the appearance of erythema, blister;
- scratch test - the imposition of an allergen on the affected area of skin; the sample is evaluated as positive the development of erythema or blister;
- Option prick tests - prick test;

Provocative tests with the application of the allergen to the mucous membranes:

- Conjunctival - the introduction of an allergen into the conjunctival sac; with a positive result, tearing, conjunctival hyperemia;
- Nasal - instillation of allergen in one nostril; with a positive result of sneezing, runny nose, difficulty breathing through the appropriate half of the nose;
- Bronchial - inhalation of the allergen in gradually increasing concentrations; with a positive result, bronchospasm, reduction in vital capacity and Tiffno factor.

Passive transfer tests with allergic antibodies - passive sensitization by intradermal injection of a healthy human patient serum (reaction Praustnica-Kyustnera). For the production of the reaction initially administered intradermally investigated serum of patients sensitized to the recipient (0.02-0.1 ml) after 24 hours in the same area of skin injected 0.02 ml of antigen; with a positive response in 10-20 minutes appear redness, swelling and itching.

Test in vitro - bioassay allergen action on a target cell:

- The reaction of basophil degranulation, mast cells, neutrophils loaded class E antibodies to allergen exposure;
- Determination of antibodies radioimmmunoallergicadsorbtion Class E - sequential processing the patient's blood serum media (paper discs) class E antibodies labeled). According to the degree of radioactivity determine the presence of allergic antibodies in the patient.

Testing delayed hypersensitivity.

Test in vivo: is produced by provocative tests with allergens (epidermal, scratch test, intradermal).

Testing in vitro aims to identify active rosette T-lymphocytes that have Fc-receptors are absent, but there IA antigen detected in T cells. Among these, there are subpopulations of T-

lymphocytes with receptors possessing high avidity to the sheep erythrocytes. Test correlates with specific allergen skin tests to test in vivo and stimulate lymphocytes.

Test of blast transformation of lymphocytes is to identify the percentage of lymphocytes that can be converted into the blasts in the 24-hour culture under the influence of allergens or PHA. The test characterizes the immunological potency of the body and makes it possible to estimate the intensity of the immune response. In a healthy person in the lymphatic mass contains 90% of small lymphocytes with transformational index of about 85%. In allergic diseases (rheumatoid arthritis, and others.) Transformation index decreased to 20%, and with lymphatic leukemia in the evolutionary stage of the disease blasts in transformation almost falls.

Suppression of macrophage migration Test - capillaries filled with suspensions of live leukocytes of a healthy donor, placed in an environment with a suspension of live leukocytes patient test in which the test is added - inhibition of macrophage release of a healthy donor from the capillary into the surrounding environment.

PRINCIPLES OF TREATMENT AND PREVENTION

As with most diseases, treatment and prevention of allergic reactions is based on the realization etiotropic, pathogenetic, and symptomatic sanogenetic principles.

Causal treatment and prevention

Causal treatment is aimed at removing the allergen from the body, and prevention - to avoid exposure of the body to the allergen.

If causal treatment measures are being taken to remove the body from germs, parasites, fungi, protozoa (sanitation) and the excretion of abnormal proteins and other allergic compounds.

When causal prevention take measures to prevent the ingestion of allergens: pollen, dust, animal fur ingredients, organic and inorganic substances, drugs, and other allergens. For this purpose, patients avoid contact with animals, plants, flowers, that they cause allergies. In production use treatment facilities, exhaust ventilation, respirators, humidification, masks, gloves and other devices to prevent entry into the body, the skin and the mucous of allergic substances.

Pathogenetic therapy

Pathogenetic therapy is aimed at breaking the basic pathogenesis of allergy and prevention - was in advance of its blockade of the potential mechanisms of development. These activities are called hypo - or desensitization of the body, because they are intended to blockade immunogenic sensitizing processes are aimed at prevention and neutralization of mediators of allergy. For this purpose, conduct specific and / or nonspecific desensitization.

- Specific desensitization is achieved by parenteral administration (as a rule, according to certain schemes) of the allergen, which is expected to cause sensitization (the method is designed for: formation of allergen complex with AT and the corresponding reduction of Ig).
- Non-specific desensitization is used in cases where specific for any reason impossible or ineffective, or when not possible to identify the allergen. It can be achieved using certain drugs (eg, antihistamine and membrane stabilizing) with immediate-type allergy; immunosuppressive drugs (including glucocorticoids), and immunomodulators - with delayed type allergy, as well as using some kind of physiotherapy effects.

Sanogenetic therapy

Sanogenetic effects are aimed at activation of protective, compensatory, reparation, replacement and other adaptive processes and reactions in the tissues, organs and the body as a

whole. For this purpose, use vitamins, adaptogens (ginseng, Siberian ginseng), is carried out non-drug measures: tempering, exercise, fasting, and others.

IMMUNOPATHOLOGY

There is a constant mutation in the human body. Some of the mutations are accompanied by the synthesis of new proteins. The structural and functional changes that occur in this connection can lead to significant disorders in the vital activity of cells, tissues, organs, and the organism as a whole. In addition, the body is constantly attacked by viruses, bacteria, rickettsia, fungi, parasites that can cause various diseases. In this connection, in the course of evolution, a highly effective system of cellular and non-cellular factors of recognizing one's own and other structures was formed.

SYSTEM OF IMMUNOBIOLOGICAL SURVEILLANCE

Biological significance of the system of immunobiological surveillance of IBS is to control (supervise) the individual and homogeneous cellular-molecular composition of the organism. Detection of the carrier of alien genetic or antigenic information (molecules, viruses, cells or their fragments) is accompanied by its inactivation, destruction and, as a rule, elimination. In this case, the cells of the immune system are able to preserve the "memory" of this agent. The repeated contact of such agent with the cells of the IBS system is accompanied by the development of an effective response that is formed with the participation of both specific immune defense mechanisms and nonspecific factors of resistance of the organism.

The concepts of AG, immunity, immune system and the system of factors of nonspecific defense of the organism are among the basic concepts in the system of the mechanisms of supervision of the individual and homogeneous antigenic composition of the organism.

ANTIGENES

The initial link in the process of forming an immune response is the recognition of a foreign agent - antigen (AG). The origin of this term is associated with the search for agents, substances or "bodies", neutralizing the factors that cause the disease, and specifically it was a toxin diphtheria bacillus. These substances were called "antitoxins" at first, and soon the more general term "antibody" was introduced. The factor, which leads to the formation of "antibodies", was designated as "antigen".

Antigen is a substance of exo - or endogenous origin, which causes the development of immune reactions.

Given the ability of AG to cause tolerance, immune or allergic response, they are also called tolerogenes, immunogens or allergens, respectively.

In some cases (under special conditions) the presence of foreign AI for the immune system is accompanied by a slight reaction of the organism to it or even by the absence of any response. This condition is called tolerance, and AG, which causes this condition, is called a tolerogen.

The different result of the interaction of the AG and the body (immunity, allergy, tolerance) depends on a number of factors: the properties of the AG itself, the conditions of its interaction with the immune system, the state of reactivity of the organism and others.

Antigenic determinant

The formation of AB and the sensitization of lymphocytes is caused not by the entire molecule of the AH, but only by a special part of it - the antigenic determinant, or epitope. In most protein AG, this determinant is formed by a sequence of 4-8 amino acid residues, and in polysaccharide AH - 3-6 hexose residues. The number of determinants of one AG may be different. So, egg albumin has at least 5 of them, diphtheria toxin has a minimum of 80, and thyroglobulin has more than 40.

Types of antigens

In accordance with the structure and origin of AG divided into several types.

1. epending on the structure distinguish between protein and non-protein AG.

- Proteins or complex substances (glycoproteins, nucleoproteins, LP) containing amino acid sequences. The molecules of these chemical compounds can carry several different antigenic determinants on their surface;
- Substances not containing protein are called haptens. These include many mono-, oligo- and polysaccharides, lipids, glycolipids, artificial polymers, inorganic substances (iodine, bromine, bismuth compounds), some drugs. The haptens themselves are not immunogenic. However, after they are added (usually covalent) to the carrier - a protein molecule or protein ligands of cell membranes, they acquire the ability to induce an immune response. The hapten molecule usually contains one antigenic determinant.

2. Depending on the origin, exogenous and endogenous AG are distinguished.

1) Exogenous hypertension is divided into infectious and non-infectious.

- Infectious and parasitic AG (viruses, rickettsia, bacteria, fungi, mono- and multicellular parasites).
- Non-infectious (foreign proteins, protein-containing compounds, AG and haptens in dust, food, pollen of plants, a number of drugs).

2) Endogenous AG (autoantigens) appear when proteins and protein molecules of own cells, noncellular structures and body fluids are damaged, when conjugated with haptens, as a result of mutations leading to the synthesis of abnormal proteins, in the event of immune system failures. In other words, in all cases when AG is recognized as foreign.

IMMUNITY

In immunology, the term "immunity" is used in three meanings.

- To denote the state of immunity of an organism to the effects of a carrier of alien genetic or antigenic information (bacteria, viruses, rickettsia, parasites, fungi, cells of foreign graft, tumors, etc.).
- To denote the reactions of the system of IBS against AG.
- To denote the physiological form of the immunogenic reactivity of the organism, which is observed when the cells of the immune system contact a genetically or antigenically foreign structure. As a result, this structure undergoes destruction and, as a rule, is eliminated from the body.

THE IMMUNE SYSTEM

The substrate for the development of the immune response are organs, tissues and cells that are functionally integrated into the immune system. The immune system is a complex of organs and tissues that contain immunocompetent cells and provides antigenic individuality and homogeneity of the organism by detection and, as a rule, destruction and elimination of foreign AG from it. The immune system consists of central and peripheral organs.

1. The central (primary) organs include the bone marrow and the thymus gland. In them, there is an antigen-independent division and maturation of lymphocytes, which subsequently migrate to the peripheral organs of the immune system.
2. The peripheral (secondary) organs include the spleen, lymph nodes, tonsils, lymphoid elements of a number of mucous membranes. In these organs both antigen-independent and antigen-dependent proliferation and differentiation of lymphocytes occur. As a rule, mature lymphocytes first contact the AG precisely in the peripheral lymphoid organs.
- The population of the peripheral organs of the immune system of T - and B - lymphocytes coming from the central organs of the immune system does not occur chaotically. Each population of lymphocytes migrates from the blood vessels to certain lymphoid organs and even to different regions. Thus, B-lymphocytes predominate in the spleen (in its red pulp as well as in the periphery of the white) and in the Peyer's patches of the intestine (in the centers of the follicles), and the T-lymphocytes in the lymph nodes (in the deep layers of their cortex and in the perifollicular space).
- In the body of a healthy person in the process of lymphopoiesis, more than 10^9 varieties of homogeneous clones of lymphocytes are formed. In this case, each clone expresses only one kind of specific antigen-binding receptor. Most of the lymphocytes of the peripheral organs of the immune

system are not fixed in them forever. They constantly circulate with blood and lymph both between different lymphoid organs, and in all other organs and tissues of the body. Such lymphocytes are called recirculating.
- Biological meaning of T- and B-lymphocyte recirculation: constant monitoring of antigenic structures of the body; Realization of intercellular interactions (cooperation) of lymphocytes and mononuclear phagocytes, which is necessary for the development and regulation of immune responses.

Immunocompetent cells

Immunocompetent cells include T- and B-lymphocytes, NK cells and antigen-presenting cells. T-lymphocytes develop in the thymus from progenitor cells. B-lymphocytes differentiate in the fetal liver and bone marrow of an adult organism. NK cells are formed from the precursors of lymphoid cells in the bone marrow. Lymphocytes, like other leukocytes, on their surface express a large number of different molecules, through which, with the help of monoclonal AB, they are identified as belonging to a specific cell population. Most often for this purpose, differentiating antigens (CD) are identified, which are specific cell markers. Among them are linear cell markers, maturation markers and activation markers.
- Linear cell markers are products of genes that are expressed only in certain cell types. An example of a linear cell marker is the CD3 molecule, which is present only in T lymphocytes.
- The ripening marker, CD1 molecule, is expressed in thymocytes and disappears later when they are differentiated into peripheral T-lymphocytes.
- IL-2 receptor - CD25 molecule - an example of an activation marker exposed on the surface of stimulated AH cells.

The identification of cell markers with AB is used in flow cytometry to sort and count the number of cells in the populations under study.

B-LYMPHOCYTES

This subsystem is formed by various clones of B-lymphocytes. The name of the subsystem reflects the fact that the lymphocytes that represent it are formed in birds in the bag (Fabiaus bursa) (for the first time B-lymphocytes were detected in the lymphoid organs of birds). In humans, there is no such bursa, B-lymphocytes mature in the bone marrow, and also, probably, in Peyer's patches, tonsils, certain zones of the spleen and lymph nodes. B-lymphocytes originate from the stem blood-forming cells of the bone marrow.

B-lymphocytes form the effector link of the humoral immune response. In the B-lymphocyte membrane, the AG-IgM monomer is present. From the red bone marrow, B-lymphocytes migrate to the thymus-independent zones of the lymphoid organs. The life span of most B-lymphocytes does not exceed ten days, unless they are activated by AG. Mature B-lymphocytes (plasma cells) produce AB-Ig of all known classes. CD 19, CD20 and CD22 are the main markers used to identify B cells.

During the formation of B-cells, the antigen-independent and antigen-dependent stages are isolated.

Antigen-independent stage

The antigen-independent stage of maturation of B-lymphocytes occurs under the control of local cellular and humoral signals from the microenvironment of pre-B lymphocytes and is not determined by contact with AG. At this stage, separate pools of genes encoding Ig synthesis are formed, as well as the expression of these genes. However, on the cytolemma of pre-B cells there are no surface receptors Ig, the components of the latter are in the cytoplasm.

The formation of B-lymphocytes from pre-B lymphocytes is accompanied by the appearance on their surface of primary Ig, capable of interacting with AG. Only at this stage B-lymphocytes enter the bloodstream and colonize the peripheral lymphoid organs. Formed young B-cells accumulate mainly in the spleen, and more mature - in the lymph nodes.

Antigen-dependent stage

The antigen-dependent stage of development of B-lymphocytes begins with the moment of contact of these cells with AG (including - allergen). As a result, activation of B-lymphocytes takes place, proceeding in two stages: proliferation and differentiation.

Proliferation of B-lymphocytes provides two important processes:

- Increase in the number of cells differentiating into AB (Ig) B-producing cells (plasma cells). With the maturation of B cells and their transformation into plasma cells, an intensive development of the protein-synthesizing apparatus, the Golgi complex, and the disappearance of surface primary Ig occur. Instead, antigen-specific ABs already secreted (ie secreted into biological fluids - blood plasma, lymph, CSF, etc.) are produced. Each plasma cell is able to secrete a large amount of Ig - several thousand molecules per second. The processes of division and specialization of B cells are carried out not only under the influence of hypertension, but also with the obligatory participation of T-lymphocytes-helpers, as well as the cytokines they release and phagocytes, growth and differentiation factors;
- The formation of B-lymphocytes of immunological memory. These B cell clones are long-lived recirculating small lymphocytes. They do not turn into plasma cells, but they retain the immune "memory" about AG. The memory cells are activated when they are stimulated again by the same AG. In this case, B-lymphocytes of memory (with the obligatory participation of helper T-cells and a number of other factors) provide a rapid synthesis of a large number of specific ABs interacting with foreign AG, and the development of an effective immune response or an allergic reaction.

T-LYMPHOCYTES

The T-lymphocyte subsystem is represented by various clones of T-lymphocytes. Their proliferation and differentiation occurs under the control of the thymus gland. In this regard, they are designated as T-cells, or thymus-dependent lymphocytes. T-cells, like B-lymphocytes, develop from the stem blood-forming cells of the bone marrow. Hence, in the form of progenitor cells, T-lymphocytes enter the thymus with blood, where their antigen-independent maturation occurs,

accompanied by the expression on the cytolemma of specific receptors (in each lymphocyte of their own).

T-lymphocytes recognize AG, previously processed and presented on the surface of antigen-presenting cells. T-lymphocytes (thymus-dependent) are responsible for the cellular immune response, and also help to respond to AB B-lymphocytes with a humoral immune response. T cells consist of functional subtypes of CD4 + and CD8 +.

T-helpers (Tn) - CD4 + T cells. Upon activation, cytokines (IL-2, IL-4, IL-5, IL-6, γ-IFN) are synthesized and secreted. In the course of the immune response, MHC class II molecules are recognized.

Cytotoxic T-lymphocytes (Tc) -CD8 + T-cells, destroy virus-infected, tumor and foreign cells with cytolytic protein-perforin. Interact with a molecule of MHC class I in the plasma membrane of the target cell.

T-suppressors (Ts) - representatives of CD8 + T cells - regulate the intensity of the immune response, suppressing the activity of Th cells; Prevent the development of autoimmune reactions; Protect the body from unwanted consequences of the immune reaction, from excessive inflammation and autoaggression.

NK-CELLS

NK cells (MHC-unreplicated killers, natural killers) account for up to 15% of all blood lymphocytes. They do not have surface determinants, characteristic for T and B lymphocytes, do not have a T lymphocyte receptor. In typical NK cells, the differentiating ABs of CD2, CD7, CD56 and CD16 (the Fc receptor of IgG) are expressed. The glycoprotein CD69 appears in the plasma membrane of activated NK cells. NK cells recognize and destroy tumor and virus-infected cells. The mechanism of recognition is unclear. There is an idea of the presence of surface-cell molecules that protect the body cells from the cytotoxic effect of NK cells. An example is the product of the

HLA-C gene. The receptor recognition of the NK cell of this molecule inhibits the cytotoxic activity of NK cells and thus protects the cell expressing HLA-C. Modification of the HLA-C gene product by viruses or tumor-associated molecules results in the destruction of this cell by an NK cell. NK cells, having an IgG receptor (CD 16), are also able to interact with cells surrounded by IgG molecules and destroy them (the phenomenon of AT-dependent cytotoxicity). Activated NK cells release γ-IFN, IL-1, GM-CSF. When activated (for example, under the influence of IL-2) NK cells acquire the ability to proliferate. Function of NK cells is disrupted in the syndrome of Shedyak-Higashi. The defect of NK cells is the cause of chronic infections.

Cytolysis. Unlike cytotoxic T-lymphocytes, the ability of NK cells to cytolysis is not associated with the need to recognize MHC molecules on the target surface. NK-cells destroy the target cell not by phagocytosis, but (after establishing direct contact with it) with perforin.

Humoral regulation. The activity of NK cells is regulated by cytokines. Γ-IFN and IL-2 enhance the cytolytic activity of NK cells.

Participation in antibody-dependent cell-mediated cytolysis. NK-cells, along with macrophages, neutrophils and eosinophils, are also involved in AB-dependent cell-mediated cytolysis. To do this, NK cells express on their surface the receptor of the Fc fragment of IgG (CD 16). The reaction depends on the presence of AT (Ig) recognizing the target cell and binding to it. The Fc fragment of these ABs interacts with the Fc fragment receptor built into the plasma membrane of the N K cell. The nature of the agent that kills the target cell in this case is unknown.

ANTIGEN-REPRODUCING CELLS

Antigen-presenting cells are present mainly in the skin, lymph nodes, spleen and thymus. These include macrophages, dendritic cells, follicular process cells of lymph nodes and spleen,

Langerhans cells, M cells in the lymphatic follicles of the digestive tract, epithelial cells of the ocular glands. These cells capture, process and represent AG (epitope) on their surface to other immunocompetent cells, produce IL-1 and other cytokines, secrete prostaglandin E2 (PGE2), inhibiting the immune response. The phagocytic and cytolytic activity of macrophages enhances γ-IFN.

Dendritic cells originate from the bone marrow and form a population of long-lived cells that trigger and modulate the immune response. In the bone marrow, their precursors form a subpopulation of SB34 + cells that are able to differentiate into Langerhans cells for the epithelium and dendritic cells for the internal environment. Immature and non-dividing progenitors of dendritic cells colonize many tissues and organs. The differentiation of dendritic cells is supported by colony-stimulating factor of granulocytes and macrophages GM-CSF and IL-3. Dendritic cells are star-shaped and in the resting state carry on the surface a relatively small number of MHC molecules. Unlike Langerhans cells, interstitial dendritic cells are able to stimulate the synthesis of Ig B lymphocytes. All dendritic cells can first enter the thymus-dependent zone of the peripheral lymphoid organs, where they mature into so-called interdigitating cells.

Interaction of cells with an immune response

The immune response is possible as a result of activation of clones of lymphocytes and consists of two phases. In the first phase, the AG activates those lymphocytes that recognize it. In the second (effector) phase, these lymphocytes coordinate the immune response aimed at eliminating AG.

HUMOR IMMUNE RESPONSE

In the humoral immune response, effector cells are antigen-presenting cells and B-lymphocytes, the T-helpers and T suppressors regulate antibody production.

Antigen-presenting cells

The macrophage absorbs the invading Ag and exposes it to processing - splitting into fragments. Fragments of AG are exposed on the cell surface together with the MHC molecule. Complex "AG-molecule MHC class II" is presented to the T-helper.

T-helpers

The T-helper recognizes the complex "AG-molecule of MHC class II" on the surface of the antigen-presenting cell. To activate the T-helper, the specific recognition of the A-helper fragment by the T-helper on the surface of the antigen-presenting cell is insufficient. Activation of T-helpers ensures the interaction of the B7 molecule (located on the surface of the antigen-presenting cell) with the CD28 molecule on the T-helper surface. Recognition of the desired molecules by the T helper on the surface of the antigen-presenting cell stimulates the secretion of IL-1. Activated IL-1 T-helper synthesizes IL-2 and IL-2 receptors, through which the agonist stimulates the proliferation of T-helpers and cytotoxic T-lymphocytes. In the case of the T-helper, it is an autocrine stimulation when the cell reacts to the agent that synthesizes and secrets itself. Thus, after interaction with the antigen-presenting cell, the T-helper acquires the ability to respond to the action of IL-2 by an increase in proliferation. The biological meaning of this process is the accumulation of so many T-helpers that will ensure the formation in the lymphoid organs of the required number of plasma cells capable of producing AB against this AG.

B-lymphocytes

Activation of B-lymphocyte suggests direct interaction of AG with Ig on the surface of the B-cell. In this case, the B-lymphocyte itself processes AG and represents its fragment in

connection with the MHC II molecule on its surface. This complex recognizes the T-helper, selected with the help of the same AG, which participated in the selection of this B-lymphocyte. Two pairs of molecules participate in the activation of the B cell: on the one hand, the specific interaction of AG with the receptor (IgM) on the surface of the B lymphocyte, and on the other hand, the CD40 molecule on the B cell surface interacts with the CD40L molecule on the T helper surface, Activating B-cell. Recognition by the T helper receptor of the AG-MHC class II complex on the B-lymphocyte surface results in secretion from the T-helper IL-2, IL-4, IL-5, and IFN-γ. Under their action, the B-cell is activated and proliferates, forming a clone. The activated B-lymphocyte differentiates into a plasma cell: the number of ribosomes increases, the granular endoplasmic reticulum and the Golgi complex become more pronounced.

Plasma cells

The plasmatic cell synthesizes Ig. IL-6, isolated by activated T-helper cells, stimulates Ig secretion. Some of the mature B-lymphocytes after AG-dependent differentiation circulate in the body as memory cells.

CELLULAR IMMUNE RESPONSE

In the cellular immune response, effector cells are cytotoxic T-lymphocytes, whose activity is regulated by T-helpers and T suppressors.

Cell-mediated cytolysis reactions

Effector cells use their receptors to recognize the target cell and destroy it. For cell-mediated cytolysis not only T-lymphocytes, but also other subpopulations of lymphoid cells, and in some cases myeloid cells, are responsible. In the process of recognition, various molecules participate on the surface of interacting cellular partners:

- Specific AG (eg, viral peptides on the surface of infected cells) in complex with MHC molecule are recognized by receptors of cytotoxic T cells, predominantly CD8 + cells and some subpopulations of CD4 + cells;
- the antigenic determinants of tumor cells are recognized by NK cells without the participation of the MHC class I molecule;

- associated with AG AB on the surface of target cells, are recognized by receptors of Fc fragments of NK cells (the phenomenon of AB-dependent cytotoxicity).

Cytotoxic T-lymphocytes

Presented on the surface of the target cell, the AG in combination with the MHC class I molecule binds to the receptor of the cytotoxic T lymphocyte. In this process, the CD8 molecule of the cell membrane Tc participates. The secreted T-helper IL-2 stimulates the proliferation of cytotoxic T-lymphocytes.

Destruction of the target cell

The cytotoxic T-lymphocyte recognizes the target cell and attaches itself to it. In the cytoplasm of the activated cytotoxic T-lymphocyte, there are small dark organelles resembling the storage granules of secretory cells. The granules are concentrated in the part of the T-killer that is located closer to the site of contact with the target cell. In parallel, the cytoskeleton is reoriented and the Golgi complex is displaced into this region, in which granules are formed. They contain cytolytic protein perforin. The T-killer molecules of perforin are polymerized in the membrane of the target cell in the presence of Ca2 +. The perforin pores formed in the plasma membrane of

target cells pass water and salts, but not protein molecules. If the polymerization of perforin occurs in the extracellular space or in the blood, where calcium is abundant, the polymer will not be able to penetrate the membrane and kill the cell. The specific action of the T-killer manifests itself only as a result of close contact between it and the target cell, which is achieved due to the interaction of Ar on the surface of the victim with the T-killer receptors. The T-killer itself is protected from the cytotoxic action of perforin. The mechanism of self-defense is unknown.

Nonspecific defense of the body

In addition to immunocompetent cells, cellular and humoral factors (constitutional factors) of the system of nonspecific defense of the organism also participate in the reactions of detection and elimination of alien molecular and cellular structures. These include phagocytic cells, factors of the complement system, kinins, IFN, lysozyme, acute phase proteins and some others.

Constitutional factors are evolutionarily the most ancient. They are extremely diverse, and the mechanisms of their functioning are variable; All these factors combine the non-specificity of the action. For example, the most simple factor of mucosal stability - the so-called "cell inactivity" - is associated with the absence of receptors on which viruses are adsorbed or toxins are fixed. Factors of nonspecific resistance are divided into mechanical, physicochemical and immunobiological. The basis of the first - anatomical barriers (skin and mucous membranes). They serve as the first line of defense against infectious agents. The structure, physical properties, secretory substances of physical and chemical barriers do not allow microbes to enter the internal environment of the body, often killing or inhibiting their growth.

MECHANICAL BARRIERS

Skin and mucous membranes effectively protect the human body from pathogens. A necessary condition for the penetration of many pathogens - microtraumas of the skin and mucous membranes, or bites of bloodsucking insects.

Skin covers are provided with "impregnable" multilayer epithelium. This "line of defense" is backed by the secrets of the skin glands and the constant sloughing off of the dead layers of the epidermis. Violation of the integrity of the epidermis (for example, in trauma or burns) is a serious prerequisite for microbial invasion, especially when contacting infected substrates (soil, plant residues, etc.). It should be remembered that in addition to the barrier role, the skin is provided with a powerful immune defense system (lymphocytes, cells of the mononuclear phagocyte system).

Mucous membranes can have special anatomical structures (for example, cilia in the ciliary epithelium of the trachea). Cilia ciliated into the mucus form waves of unidirectional oscillations and move the mucus with particles enclosed upwards (to the exit of their respiratory tract) along the surface of the epithelium (the process of mucociliary transport).

Some constitutional protective barriers

Tissues or organs	Types of cells	Mechanisms of elimination of microorganisms
Physical		
Skin	Epidermis (also a multilayer epithelium of mucous membranes)	Mechanical delay, sloughing of cell layers
Mucous membranes	Chamomile epithelium	Inhibition of adhesion of microorganisms
	Ciliary epithelium	Mucociliary transport
	Different epithelium	Mechanical delay and rinsing with saliva, tear fluid, secrets

	Secretory	Isolation of secretion, washing off microbes
Chemical		
Skin	Sweat and sebaceous glands	Organic acids (acidification of the medium)
Mucous membranes	Parietal cells of the stomach	Hydrochloric acid (bactericidal action)
	Secretory cells	Bactericidal and bacteriostatic substances
	Polymorphonuclear leukocytes	Lysozyme, free radicals, lactoferrin
Lungs	Alveolocytes	Surfactant
	Alveolar macrophages	Phagocytosis
Upper GI tract	Salivary glands	Thiocyanates
	Polymorphonuclear leukocytes	Lysozyme, myeloperoxidase, lactoferrin, cationic proteins
Lower GI tract	Bile	bile acid
	Normal microflora	Toxic low molecular weight fatty acids

PHYSICAL AND CHEMICAL FACTORS

The mechanical barrier properties of the skin are supplemented with the secrets of the skin glands; The latter show direct bactericidal activity, or reduce the pH of the skin to unfavorable values due to the secretion of acids (acetic, lactic, etc.).

Mucous membranes

Mucous membranes have many protective factors - from acidic pH values of the stomach to the secretion of enzymes and AB.

- Slime. Mucous membranes are covered with a layer of mucus - an organized gel-like glycoprotein structure that retards and fixes various objects, including microorganisms. The mucus is hydrophilic; Through it, many substances formed in the body can diffuse, including bactericidal substances (for example, lysozyme and peroxidases).
- Lysozyme. In detachable mucous membranes contains lysozyme - an enzyme lysing the cell walls of predominantly Gram-positive bacteria. Lysozyme is present in other body fluids (for example, in saliva, tear fluid).
- Surfactant. In the lower parts of the airways and the respiratory department there is no mucus, but the surface of the epithelium is covered with a layer of surfactant, a surfactant capable of fixing and destroying gram-positive bacteria.
- Immunoglobulins. On the surface of the epithelium of the gastrointestinal tract and the respiratory tract, molecules of secretory IgA are constantly secreted.

FLAMMATION

If the causative agent overcomes surface barriers, it is met by factors of the second, immunobiological line of nonspecific defense mechanisms. Such protective mechanisms are usually divided into humoral and cellular. A complex of constitutional mechanisms for the protection of tissues - an evolutionarily ancient form of organized protection - the precursor of induced (immune) reactions. This is confirmed by the fact that a significant part of the

constitutional components of protection are inducible and are in tissues in an inactive form. Their activation is caused by various mediators of inflammation. A key role in nonspecific protection of the internal environment of the body is played by complement and phagocytic cells. Their activity is largely complemented by various BAS.

Inflammation is a complex of protective-adaptive reactions that arises in response to damage or pathological stimulation caused by a physical, chemical or biological agent. Subsequently, tissues can completely restore their structure and functions, or they form permanent defects. Often acute inflammation changes its characteristics and takes a chronic course. Most reactions of acute inflammation significantly alter the lymph - and blood circulation in the focus of inflammation. Vasodilatation and increased capillary permeability facilitate the escape from the lumen of the capillaries of macromolecules (for example, complement components) and polymorphonuclear fagocytes, that is accompanied by the formation of exudate. With a moderate inflammatory reaction, the exudate contains a small amount of protein (serous exudate); With a more intensive reaction, the protein content (for example, fibrinogen) sharply increases (fibrinous exudate). The mechanisms of coagulation are aimed at the formation of fibrin clots, which prevent dissemination of the pathogen with blood and lymph. An important factor of protection is a decrease in pH in tissues due to inflammation caused by the secretion of lactic acid by phagocytes. Acidosis has a harmful effect on bacteria and reduces resistance to antimicrobial chemotherapy drugs. Inflammation begins with the activation of complement and hemostasis systems. Many components of these systems are mediators of inflammation.

Histamine, the main mediator of inflammatory reactions, causes an expansion of the superficial venules of the skin and mucous membranes, an increase in vascular permeability and stimulation of terminals of sensitive type C neurons (pain impulses, activation of which causes itching and pain), releasing neuropeptides (substance P) in the posterior horns of the dorsal Brain. The release of histamine from mast cells and basophils induce IgE-dependent mechanisms, various substances (opiates, aminoglycosides) and anaphylatoxins (components of the complement system C3a and C5a).

Kinin - low molecular weight peptides (oligopeptides), increasing vascular permeability and releasing mediators polymorphonuclear phagocytes. The predecessors of kinin are kininogens (high molecular weight proteins). Proteolysis of kininogens with the formation of kinins is carried out by kallikreins - specific proteases of polymorphonuclear phagocytes. The key substratum of these reactions is Hageman's factor, which plays an important role in the clotting reactions.

Leukotrienes and prostaglandins, as well as their metabolites, are the main mediators of acute inflammation. Increase the permeability of blood vessels, cause a decrease in HMC. Leukotriene B4 activates the chemotaxis of polymorphonuclear phagocytes; Thromboxane A2 induces aggregation of platelets, and prostaglandins, acting on the hypothalamus, cause an increase in body temperature. In addition, prostaglandins affect the nerve endings of type C fibers - that's why stimuli, which normally do not cause pain reaction, provoke a pain attack during inflammation.

Proteins of the acute phase of inflammation. The inflammatory reaction is accompanied by the release of various proteins (mainly from the liver), also performing mediator functions. They are united by the common term "proteins of the acute phase of inflammation". The most known C-reactive protein, lipopolysaccharide-binding protein, serum amyloid protein A, α1-antitrypsin.

Cytokines. Many bacterial products activate cells of the mononuclear phagocyte system and lymphocytes; These cells respond to the release of the BAS complex. Such factors are referred to

as two large classes - cytokines (subclasses: interleukins, interferons, growth factors, colony-stimulating factors of hemopoiesis) and chemokines (chemoattractants). So, at least 18 interleukins

(IL) are known. Most of them are also mediators of immune reactions. In inflammatory reactions, the main role is played by IL-1, stimulating febrile reactions, increasing vascular permeability and adhesive properties of the endothelium, as well as activating mono- and polymorphonuclear phagocytes.

THE COMPLEMENT SYSTEM

The complement system is a group of at least 26 serum proteins (complement components) mediating inflammatory responses involving granulocytes and macrophages. System components participate in blood clotting reactions, promote intercellular interactions necessary for AG processing, cause lysis of bacteria and cells infected with viruses. Normally, the components of the system are inactive. Activation of complement leads to alternate (cascade) appearance of its active components in a series of proteolytic reactions that stimulate protective processes. The main functions of complement components in protective reactions are stimulation of phagocytosis, disruption of the integrity of cellular walls of microorganisms by a membrane-damaging complex (especially in species resistant to phagocytosis, for example, gonococci) and induction of the synthesis of inflammatory response mediators (eg, IL-1). In addition, the complement system stimulates inflammatory reactions (some components - chemoattractants for phagocytes), participates in the development of immune (via activation of macrophages) and anaphylactic reactions. Activation of complement components can take place along the classical and alternative paths.

The classical way

Activation of complement on the classical pathway by AG-AB complexes. Includes alternate formation of all 9 components (from C1 to C9). The components of the classical path are denoted by the Latin letter "C" and the Arabic numerals (C1, C2 ... C9), for the complement subcomponents and cleavage products, lowercase Latin letters (Clq, C3D, etc.) are added to the corresponding designation. Activated components are highlighted with a line above the letter, inactivated components by the letter "i" (for example, iC3b). Initially, O (subcomponents Clq, Clr, C Is) interacts with the AG-AT complex, then the "early" components C4, C2, and C3 join them. They activate the C5 component that binds to the target cell membrane (bacteria, tumor cells or virus-infected cells) and triggers the formation of a lytic complex (C5b, C6, C7, C8 and C9). Otherwise, it is called a membrane-damaging (membrane-attacking) complex, since its formation on the membrane causes destruction of the cell. Examples of microbial products that activate the complement system along the classical pathway are DNA and protein A of staphylococci.

Alternative path

Activation of complement on the alternative path occurs without the participation of AT and long before their appearance. The factors of the alternative path have the letter designation: P (properdin), B and D (enzymes of the complement system). The activation of the alternative pathway activates the C3 component interacting with factors B and D. Then, through the formation of component C5 (but without the participation of CI, C2 and C4), the alternative pathway also terminates by the formation of a membrane-damaging complex on the surface of target cells. An alternative pathway is activated by microbial products such as bacterial endotoxins, viruses (eg, influenza).

PHAGOCYTATIC CELLS

Phagocytes perform not only protective (absorb and destroy foreign agents), but also drainage functions (remove deceased and degraded body structures). Phagocytes are represented by cells of myelopoietic series (polymorphonuclear leukocytes) and macrophage-monocyte system (monocytes, tissue macrophages).

Phagocytosis is the process of absorption and digestion by phagocytes of microorganisms, other cells, fragments of necrotic tissue and foreign particles. Mechanisms of activation of both

pes of phagocytes (polymorphonuclear leukocytes and monocytes / macrophages) are fundamentally the same. Activating stimuli can be bacterial products (eg, LPS, N-formyl peptides, etc.), complement components (eg, C3 and C5), many cytokines and AT receptors to which are present on the membranes of phagocytes. Phagocytosis consists of four consecutive stages: chemotaxis, attachment to the object, absorption and destruction.

Chemotaxis is an amoeboid movement of phagocytes along the concentration gradient of activating stimuli (chemotaxins, or chemotaxis factors). The property of activating the migration of macrophages is C3b, C5a, C5b, C6-, C7- and Ba-components of complement, bacterial lipopolysaccharides, cell degradation products, chemokines. The rate of attraction of cells in chemotaxis is easy to imagine, estimating, for example, the time of formation of pus and its volume after getting a splinter.

Characteristics of phagocytic cells

Cells	source	Forms of participation in protective reactions
Neutrophils	Bone marrow; After differentiation go into the bloodstream	Adhesion to the endothelium and outflow; Chemotaxis; absorption; Degranulation; Secretion of dependent and independent microbicidal factors
Eosinophils	Same	The secretion of dependent and independent microbicidal factors directed against parasites (protozoa and helminths)
Monocytes	Bone marrow; After differentiation, promonocytes enter the bloodstream	Adhesion to the endothelium and outflow; Chemotaxis; absorption; Degranulation; Secretion of dependent and independent microbicidal factors (including cytokines)
Macrophages (Kupffer cells, alveolar macrophages, histiocytes, peritoneal macrophages, microglial cells, spleen macrophages, etc.)	Peripheral blood monocytes	Adhesion to the endothelium and outflow; Chemotaxis; absorption; Degranulation; Secretion of dependent and independent microbicidal factors; Synthesis of complement components, plasminogen activator and other proteases; Secretion of mediators and components of cell membranes, including products of classes I and II of the MHC; Participation in immune reactions

Adhesion. One of the conditions for successful absorption of the pathogen is effective adhesion to the microbe. Flagellum allows microbes to move rapidly in the liquid phase, and phagocytes do not know how to "swim", but they "run" well, that is, they can only absorb their absorbing properties on any dense surface (for example, on epithelium). Opsonins, such as AB, C3B, fibronectin, surfactant, envelop microorganisms and significantly limit their mobility.

Opsonins make absorption more efficient, which is related to the stability of the interactions of opsonins with the corresponding receptors (for Fc fragments AB, complement components, fibronectin, etc.) on the phagocyte membrane. The absence of these receptors leads to a sharp decrease in the functional activity of phagocytes (for example, congenital deficiency of C3B receptors is accompanied by a high incidence of bacterial infections and even isolated into a separate nosological form - lack of leukocyte adhesion).

Absorption. The absorption of microbes is identical to that of amoebas; As a result, a phagosome with a phagocytosis inside the object is formed. Lysosomes rush towards the phagosome and line up along its perimeter. Then the membranes of the phagosome and lysosomes merge (phagosomysosomal fusion), and the lysosome enzymes are poured into the formed phagolysosome. Absorption is facilitated by the interaction of surface receptors of phagocytes with AG or fragments of opsonins sorbed on the surface of the bacterium. This reaction resembles the action of a lightning bolt (the so-called zipper absorption mechanism [from English zip, lightning bolt]). Phagocytosed microorganisms are attacked by a complex of various microbicidal factors, divided into oxygen-dependent and oxygen-independent ones.

Oxygen-dependent microbicidal activity is realized through the formation of a significant number of toxic products, damaging micro-organisms and surrounding structures. NADP oxidase (flavoprotein cytochrome reductase) of the plasma membrane and cytochrome b are responsible for their formation; In the presence of quinones, this complex transforms O2 into an anion of superoxide (02 ~). The latter exhibits a pronounced damaging effect, and also rapidly transforms into hydrogen peroxide. Hydrogen peroxide (H202) shows a less damaging effect, but in its presence, the myeloperoxidase enzyme converts C1 ~ ions into HC1O ~ ions, which have a bactericidal action, in many respects similar to the chloric lime effect (NaCIO).

Oxygen-independent mechanisms are activated as a result of the contact of the opsonized object with the phagocyte membrane. In the process of phagosomolyzosomal fusion, granules containing lactoferrin and lysozyme merge first with the phagosome membrane, then azurophilic granules containing cationic proteins (for example, CAP57, CAP37), proteinases (for example, elastase and collagenase), cathepsin G, defensins and Etc. These products cause damage to the cell wall and the disturbance of certain metabolic processes; To a greater extent, their activity is directed against gram-positive bacteria.

Completeness of phagocytic reactions. Absorbed by phagocytes, bacteria usually die and are destroyed. Some bacteria, provided with capsules or dense hydrophobic cell walls, can be resistant to the action of lysosomal enzymes; Another part of the pathogens is able to block the fusion of phagosomes and lysosomes. In such cases phagocytosis is incomplete, and the causative agent survives in the cytoplasm of the cell that has absorbed it. Many facultative and obligate intracellular parasites not only retain viability within cells, but also are able to reproduce. The persistence of pathogens is mediated by three main mechanisms.

Blockade of phagosome-hysosomal fusion. A similar mechanism is noted in viruses (eg, influenza virus), bacteria (eg, mycobacteria) and protozoa (eg, toxoplasm).

Resistance to lysosomal enzymes (eg, gonococci and staphylococci).

The ability of pathogenic microorganisms to quickly leave the phagosomes after absorption and stay in the cytoplasm for a long time (for example, rickettsia).

Other protective functions of phagocytes

- Initiation of immune reactions. Absorbing foreign agents macrophages "processed" (so-called processing AG) and "represent" (presentation) of AH immunocompetent cells. In doing so, they release cytokines that activate lymphocytes. In other words, macrophages - AG-processing and AG-representing cells, and phagocytosis can be considered as a visible reflection of these immune functions.

- Antibody dependent cytolysis. Phagocytes are involved in antibody-dependent cell-mediated cytolysis. For this, the cells express on their surface the receptor of the Fc fragment of IgG (CD 16).

OTHER FACTORS OF NON-SPECIFIC RESISTANCE

Interferons

The interferon system (IFN) is the most important factor of nonspecific resistance of the human body. It should be noted that the opening of IFN A. Isaacs and J. Lindenmannom (1957) was the result of a brilliant chance, comparable in importance with the discovery of penicillin by Fleming: studying the interference of viruses, the authors drew attention to the fact that some cells become resistant to reinfection with viruses. Currently, IFN is classified as a class of inducible proteins of vertebrate cells. Their most important functions: antiviral, antitumor, immunomodulating and radioprotective. There are three IFN: α-IFN synthesizes peripheral blood leukocytes (formerly known as leukocyte IFN); (3-IFN synthesized fibroblasts (formerly known as fibroblast interferon); γ-IFN - product of stimulated T-lymphocytes, NK-cells, and (possibly) macrophages (formerly known as immune interferon) As a method of forming distinguish IFN type I (. produced in response to treatment of cells with viruses, double stranded RNA molecules, and polynucleotides next low molecular compounds of natural and synthetic) and IFN type II (produced

lymphocytes and macrophages activated by different inducers; acts as a cytokine) species-specific IFN Each b.. ologichesky species capable of their formation, produces its own unique products that are similar in structure and properties, but not be able to cross the antiviral effect (i.e., operate in a different type of organism).

The mechanism of antivirus action. IFNs induce the "antiviral state" of the cell (resistance to penetration or blockade of the reproduction of viruses). The blockade of reproductive processes during the penetration of the virus into the cell is due to the inhibition of viral mRNA translation. In this case, the antiviral effect of IFN is not directed against specific viruses; That is, IFN does not possess virus-specificity. This explains their universally wide range of antiviral activity. IFN interact with intact, yet uninfected cells by inhibiting the realization of the reproductive cycle of the virus due to the activation of cellular enzymes (protein kinases).

IFN I. The main biological effect is suppression of the synthesis of viral proteins; Can influence other stages of reproduction of virus particles, including budding of daughter populations. The "antiviral state" of a cell develops within a few hours after the administration of interferons or induction of their synthesis. At the same time, interferons do not affect the early stages of the replicative cycle (adsorption, penetration and "stripping" of viruses) - the antiviral effect is manifested even when the cells are infected with infectious RNA. IFNs do not penetrate cells, but interact with specific membrane receptors (gangliosides or similar structures containing oligosugars). By binding IFN to the receptor and realizing its effects, the mechanism of activity resembles the action of certain glycopeptide hormones. IFN activates genes, some of which encode the formation of products with a direct antiviral effect - protein kinase and oligoadenylate synthetase.

IFN II ((3-IFN) is also capable of exhibiting an antiviral effect.It is associated with several mechanisms.First, activation of interferon N0 synthetase leads to an increase in the intracellular content of nitric oxide inhibiting the multiplication of viruses.Further, IFN activates the effector functions of NK Cells, T-lymphocytes, monocytes, tissue macrophages and granulocytes, which display antibody-dependent and antibody-independent cytotoxicity .In addition, IFN blocks the deproteinization ("stripping") of viruses, the release of mature viral particles from the cell, And

also disturbs the methylation of viral RNA.In mixed cultures of IFN-sensitive and IFN-resistant cells, the "antiviral state" of sensitive cells extends to populations of resistant cells.

Natural AB

Natural AB ("antigen-independent", "nonspecific" AB) accounts for up to 7% of the total Ig in the blood serum of nonimmunized humans and animals. Their origin is associated with the response of the immune system to AG normal microflora. The same group includes AB, which circulates long after recovery from an infectious disease. Part of a pool of similar ABs is synthesized in parallel with the formation of specific AB. The need for their appearance remains unclear. These ABs are low-specific, but are capable of cross-reacting with a wide range of AG. They cause agglutination of microbes, their destruction (in the presence of complement), neutralize viruses and toxins, and stimulate phagocytic reactions (through opsonization of pathogens).

Natural killers

In addition to phagocytic cells, natural killers (NK cells) play an important role in the rapid response of the body to foreign AG. This population consists of large granular lymphocytes, eliminating auto -, allo and xenogeneic tumor cells; Cells infected with viruses and bacteria, as well as protozoa. NK cells do not have major markers of lymphocytes (therefore they are also called zero lymphocytes), but they express differentiating CD2, CD56 and CD16 (Fc fragment of AB) AG. In contrast to cytotoxic lymphocytes, the ability of NK cells to cytolysis is associated with self-recognition of "one's own" on the surface of the target. NK cells destroy the target cell after establishing direct contact with it using special proteins - perforin. Perforins are embedded in the membrane of an alien or transformed cell, forming a "hole" in it, leading to irreversible and fatal alignment of the onic composition between the cytoplasm and the external environment. The ctivity of NK cells regulates cytokines (γ-IFN and IL-2 increase their cytolytic activity). Along with macrophages, neutrophils and eosinophils, they also participate in antibody-dependent cell-mediated cytolysis. To do this, NK cells express on their surface the receptor of the Fc fragment of IgG (CD 16). The reaction depends on the presence of AB, which recognizes the target cell and binds to it. The Fc fragment bound to the target cell AB interacts with the Fc fragment receptor embedded in the plasma membrane of the NK cell. The nature of the agent that kills the target cell in this case is not known.

IMMUNOPATHOLOGICAL STATES AND REACTIONS

Disorders of mechanisms of IBS for individual and homogeneous body composition are manifested by various immunopathological states and reactions.

1. Immunodeficiency conditions,
2. Pathological tolerance,
3. "Graft versus host" reactions,
4. Allergic reactions,
5. The state of immune auto-aggression.

Immunodeficiency states, pathological tolerance, graft versus host reactions are the result of a defect or disruption in the activity of one or more links of the IBS system, which normally provide an effective immune response.

Etiology

Immunopathological conditions can be primary or secondary.

1) The cause of primary disorders is inherited or inherited defect of the genetic program of immunocompetent cells, as well as cells that provide nonspecific defense of the body.

2) The cause of secondary disorders are disorders that occur after birth at different stages of the ontogenesis of the individual. They develop as a result of damage to the cells of the IBS system, which had a normal genetic program, under the influence of factors of different nature:

- Physical (for example, a high dose of X-rays or free radicals).
- Chemical (in particular, cytostatic agents or peroxide compounds).
- Biological (for example, a significant increase in blood glucocorticoids, damage to cells of the immune system by viruses, bacteria, foreign cells and AB).

Pathogenesis

The pathogenesis of immunopathological conditions is complex and has several development options.

1. Hyporegenerative. This variant pathogenesis (for example, immunodeficiency and pathological tolerance) is to inhibit the proliferation of stem hemopoietic and / or pluripotent, as well as other proliferating progenitor cells of the immune system. As a result, the dementation (removal) of a clone of cells of the IB system is observed in the body, as well as a more or less decrease in the total number of immunocytes and other factors of the IBS system.

2. Disregulatory. This mechanism of immunity disorders is caused by disorders of differentiation of antigen-presenting cells and / or T- and / or B-lymphocytes, as well as the co-operation of these cells.

Causes

- Change in the ratio of the number and / or effects of different categories of immunocompetent cells (eg, an increase in the number of suppressors or a decrease in the number of helper and inducers).
- Violation of the content of BAS (cytokines of different classes, corticosteroids, anabolic steroids, etc.) or the number or sensitivity of receptors to them on the membranes of immunocytes, leading to immunodeficiency and pathological tolerance.

3. Destructive (cytolytic). This variant of pathogenesis consists in massive destruction of immunocytes.

es

- Defect of the immunocytes themselves (as a consequence of membrane and / or enzymopathy).
- Effects on the immunocompetent cells of cytolytic agents (eg, AT, membrane-complement complex of complement, large doses of cytostatics, glucocorticoids, etc.). With massive destruction of immunocytes, leukopenia and various immunopathological conditions develop.

IMMUNODEFICIENCIES

Immunodeficiency - a condition characterized by a decrease in immunological reactivity as a result of a hereditary or acquired defect of effector mechanisms of immunity.

Immunodeficiencies can be defined as pathological conditions accompanied by a defect in one or more links of the immune system, and manifested in increased susceptibility to diseases, the probability of occurrence and development of which is unlikely if the immune response is normal.

Human immune responses to various effects are represented by 4 components [(cellular antigen-specific immune response (T-LYMPHOCYTE), humoral antigen-specific immune response (B-LYMPHOCYTE), complement system and cells providing phagocytosis (neutrophils and macrophages).] Deficient The functioning of the first two components of the immune system leads to diseases accompanied by disorders of the adaptive (ie, specific) level of the immune response.The deficiency and / or decrease in the functional activity of the proteins of the complement or phagocytic system Of the unit are the causes of diseases accompanied by violations of the natural (ie, non-specific) link of the immune response.

Collecting anamnesis of the patient is very valuable for a preliminary assessment of the localization of a defect in the immune system. For example, frequent repeated diseases caused by pyogenic bacteria indicate a violation of the humoral link of the immune system (B-LYMPHOCYTE), the complement and phagocytic system, and the phagocytosis system. At the same time, frequent viral diseases suggest the presence of disorders of the cellular system of the immune system (T-LYMPHOCYTE).

Further laboratory studies (evaluation of the immune status with determination of the content of various subpopulations of lymphocytes, serum immunoglobulin levels, neutrophil phagocytic activity, complementarity of the proteins in the hemolytic erythrocyte reaction, etc.) allow more accurate characterization of the possible spectrum of disorders in the functioning of the immune system of each patient.

ETIOLOGY

Primary immunodeficiencies are manifested by the development of infectious damage to the body soon after birth, but may not have clinical manifestations until later in life.

Cause

Genetic and chromosomal defects (multiple immunodeficiencies of different classes). Secondary immunodeficiencies, or immunodeficiency states

The causes of immunodeficiency states are manifold, they are:

- Immunosuppressive drugs (including phenytoin [diphenin], penicillamine, glucocorticoids).
- Insufficiency of nutrition, cavitary and membrane digestion, as well as intestinal absorption.
- Drugs and toxic substances.
- Radiation exposure, chemotherapy.
- Growth of malignant tumors.
- Viruses (eg, HIV).
- Conditions leading to loss of protein (eg, nephrotic syndrome).
- Hypoxia.
- Hypothyroidism.
- Uremia.
- Aspens.

General manifestations of immunodeficiencies

1. **Infectious**, which are manifested:
   - development of autoinfections caused by opportunistic pathogens by normal components of the intestinal microflora, respiratory, urinary tract, skin, and
   - frequent infectious diseases (eg, ARI, tonsillitis, enteritis, etc.);
   - severe and prolonged course of common infectious diseases with the development of uncharacteristic complications (for example, the development of sepsis in pneumococcal pneumonia, generalized herpetic infection, etc.);
2. **Tumor** (due to a violation of the function of "immune surveillance").
3. **Autoimmune**, (develop as a result of violations of immunological tolerance in immunodeficiencies affecting the function of T-helper type 3 (T-suppressor), the ability of the immune system to distinguish between "one's" and "someone else's" is violated).
4. **Allergic** (with deficiency of T helper type 3 (T-suppressor), the ability to adequacy, self-limitation and self-regulation of the immune response is violated).
5. **Dyshormonal** (due to a violation of the ability of the immune system to regulate the action of hormones on peripheral tissues).

Characteristic changes in immunological tests that detect cellular and / or humoral immune status defects.

TYPES OF IMMUNODEFICIENCES

Distinguish primary (congenital) immunodeficiencies, usually having hereditary nature and secondary (acquired), caused by various effects (viral and bacterial infections, tumors, immunosuppressive therapy, eating disorders, the effects of ionizing radiation, etc.). It is difficult to draw a clear boundary between them, since the susceptibility to the action of immunosuppressive factors and, consequently, to the development of secondary immunodeficiencies, can also be caused genetically.

The basis of primary (hereditary) immunodeficiencies are chromosomal rearrangements, or mutations of genes that determine immunologically significant factors or are responsible for the formation of immune system organs in ontogenesis. Theoretically, immunodeficiency should be considered primary if localization of a genetic defect and the type of its inheritance are established, where the defective gene is characterized by high penetrance (i.e., manifestation) in the form of an immunodeficiency state, an additional, albeit not mandatory, condition is the early expression of a genetic defect. In reality, these conditions are not always met. First, the localization of genetic breakdowns is not yet established for all cases of immunodeficiency, the hereditary nature of which is beyond doubt. Secondly, some examples are known when, in such diseases, it is not possible to establish the nature of inheritance (Di Georgi syndrome - hypoplasia of the thymus). A consequence of the incomplete study of the genetic basis of these diseases is an insufficiently clear division of them into specific syndromes; Some known nosological forms are actually groups of diseases (for example, a common variable immunodeficiency).

Undoubtedly, secondary immunodeficiency is the overwhelming number of immunodeficiency states, while primary immunodeficiencies are rare diseases: their total frequency is 1: 1 million, or 3 cases per 1000 clinically ill. These diseases occur almost exclusively in childhood, since a significant number of patients do not survive to 20 years, while in others, defects are to some extent compensated or treated in the context of normal infectious or somatic pathology. In the last decade, thanks to the success of treatment (primarily antibiotic therapy), this upper age threshold has been blurred, and it is hoped that due to gene therapy, the life expectancy of patients will increase significantly.

Classification of immunodeficiencies

There are 5 types of immunodeficiency states, each of which can develop as a result of congenital anomaly (primary immunodeficiency) and various lifetime effects (secondary immunodeficiency).

1. mmunodeficiencies due to insufficiency of the humoral part of the immune system A. Primary

- Transient (transient) agammaglobulinemia in children
- Agammaglobulinemia linked to the X chromosome (Bruton's disease)
- Total Variable Immunodeficiency
- Selective deficiencies of IgA, IgM and subclasses of IgG

- hypogammaglobulinemia (for example, due to loss of Ig in urine with nephrotic syndrome). 2. Immunodeficiencies due to insufficiency of the cellular system of the immune system

A. Primary

- syndrome di Georgie
- Deficiencies of adenosine deaminase and purine nucleotide phosphorylase
- the syndrome of "bare lymphocytes"

- viral infections (HIV-1, measles)
- bacterial infections (mycobacteria, etc.)
- Protozoal infections

- tumors
- uremia
- burn disease

3. Immunodeficiencies due to combined defects of the cellular and humoral parts of the immune system

A. Primary

- Severe combined immunodeficiency - Wiskott-Aldrich Syndrome
- Ataxia-telangiectasia B. Secondary
- chronic nonspecific lung diseases - micronutrient deficiency
- chemotherapy - irradiation
- fasting

4. Immunodeficiencies due to insufficiency and weakening of the function of proteins of the complement system.

A. Primary

- selective deficiency of complement components and their inhibitors (angioneurotic edema, lupus syndrome, Neisseria infection, repeated pyogenic infections, nocturnal paroxysmal hemoglobinuria) B. Secondary
- due to the rapid activation of complement components and their subsequent destruction - decrease in the synthesis of individual components (cirrhosis, malnutrition)

5. Immunodeficiencies associated with deficiency of phagocytic function

- chronic granulomatous disease
- Chediak-Higassi syndrome
- syndrome of "lazy" leukocytes
- Schwartzmann's syndrome

- deficiency of opsonins and chemotaxis factors
- chemotherapy
- tumors
- immunosuppressive therapy and glucocorticoids.

Immunodeficiencies due to insufficiency of the humoral part of the immune system

Characteristic signs of weakening in the functioning of the humoral link of the immune

system is the inability of the body to produce antibodies that have the ability to: a) inactivate bacteria and toxins in the body fluids - IgM and IgG; b) prevent the penetration of pathogens through the mucous membranes of the respiratory and digestive tracts - IgA. As a consequence, patients with this form of immunodeficiency are susceptible to pyogenic infections caused by encapsulated microorganisms (Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and various types of Pseudomonas). At the same time, insufficiency of the humoral link of the immune system does not have a significant effect on the susceptibility to diseases caused by protozoa, fungi intracellular bacterial pathogens (Mycobacteria) and viruses. An exception to this rule are diseases caused by enteroviruses.

The mechanism of increased susceptibility to pyogenic infections in persons with disorders of the humoral link of the immune system is due to the fact that pyogenic bacteria having a lipopolysaccharide shell can not be receptor-mediated by neutrophils and macrophages. That is why this type of pathogen deviates from the cellular factors of natural resistance. Effective elimination of this type of pathogens from the body entirely depends on their preliminary opsonization (antibody, complement protein), which ensures their subsequent phagocytosis. The inadequacy of antibody production in the mucous membranes (IgA) reduces the likelihood of

neutralization of viruses, which makes people with an impaired humoral immune response susceptible to enterovirus infections.

A. Primary immunodeficiency of the humoral unit

1. Transient agammaglobulinemia in children - develops between 1 and 2 years of life, due to the gradual destruction of maternal IgGs that have passed through the placental barrier. It is the result of blockade of B-LYMPHOCYTE maturation in plasma cells (normal serum IgM and IgA level and reduced IgG level) due to intercellular interactions between T and B-LYMPHOCYTE. The result of the failure of the humoral link of the immune system are frequent infections of the upper respiratory tract and middle ear. The IgG level usually normalizes to 2-4 years of a child's life.

2. Agammaglobulinemia, linked to the X chromosome (Bruton's disease) - manifests a sharp decrease (up to complete absence) in the serum of all classes of immunoglobulins. It is the result of blockade of differentiation and maturation of pre-B cells, which leads to the absence of B-Lymphocyte and plasma cells in the body. The reason for the absence of antibody producing cells is the mutation of the gene encoding tyrosine kinase btk (Bruton's tyrosine kinase), which normally normalizes the expression of the corresponding receptor on pre-B cells, which makes them sensitive to factors that ensure their subsequent differentiation. The T-LYMPHOCYTE function is not violated. Symptoms of the disease begin to develop after the expiration of the life of the parent antibodies (IgG) that have passed the placental barrier. Therapy of this disease can consist in the introduction of immunoglobulins and antibiotic therapy in the presence of bacterial infections.

3. General variable immunodeficiency - manifested in a significant decrease in the level of serum immunoglobulins against a background of normal B-LYMPHOCYTE content, the absence of germinal centers and plasma cells in the lymph nodes and spleen. It is the result of blockade of maturation of B-Lymphocyte in plasma cells (ie, the maturation block occurs at a later stage in comparison with agammaglobulinemia linked to the X chromosome). Symptoms of the disease are typical for this group - frequent sinusitis, otitis, respiratory disease caused by encapsulated pathogens). Nevertheless, the symptoms develop gradually and reach a maximum by 15-20 years of life. People with common variable immunodeficiency have a tendency to develop autoimmune diseases, chronic respiratory diseases, diarrhea and malabsorption. 1/3 of patients with variable immunodeficiency have also disorders of the cell link. Principles of therapy of persons with this pathology are similar to those of persons with hypogammaglobulinemia linked to the X chromosome.

4. Selective deficiencies of IgA, IgM and subclasses of IgG

Among the selective deficiencies of immunoglobulin isotypes, IgA deficiency is the most frequent. With this pathology in the body there are B-lymphocytes carrying membrane IgA (ie, the process of switching isotypes is carried out). Nevertheless, the formation of plasma cells secreting IgA does not occur. It is the result of a block of differentiation of mature B-Lymphocyte in IgA-producing plasma cells. Perhaps the cause of this defect is the inadequacy of signaling from T-lymphocytes, other microcirculation cells and a deficiency of the factors produced by them, especially those that contribute to the production of IgA (TGF-b and IL-5). Persons with this form of immunodeficiency are most sensitive to the development of chronic respiratory diseases. In 1/3 patients with a slight decrease in the level of IgA, these symptoms are absent, which is probably due to the compensatory capabilities of the humoral immune system in the presence of a normal level of IgG and IgM in the serum of this group of people. In individuals with a significant decrease in IgA, frequent recurrences of respiratory and gastrointestinal tract infections, an increased incidence of bronchial asthma, and autoimmune diseases are observed. It should be noted that the pronounced IgA deficiency in these patients predisposes to the production of anti-IgA antibodies, which can play a role in the development of anaphylactic reactions in the transfusion of blood or its components. Therefore, for transfusions, only "purified" erythrocytes or sera from patients with a similar pathology are suitable. Individuals with moderate selective IgA deficiency do not need

specific treatment, since normal levels of IgG and IgM "close" the gap in the immune response. The introduction of IgA is not effective because of: a) a short halymphocyte-life, b) its inability to penetrate the mucous membranes, c) the risk of developing anaphylactic reactions.

Selective IgG deficiency can affect all subclasses of IgG and can occur against a background of normal or even elevated levels of total IgG in serum. Normally, IgG1 and IgG2 are 70% and 20% of total serum IgG. The production of each subclass of IgG depends on the type and structure of the antigen. For example, the synthesis of IgG1 and IgG3 occurs on protein antigens, while IgG2 is produced by antigens that include polysaccharide and / or carbohydrate components. Consequently, in individuals with selective IgG2 deficiency there is a greater likelihood of developing sinusitis, otitis and pneumonia, the causative agents of which are bacteria whose liposuction is lipopolysaccharides (S. pneumoniae, H. influenzae type b and N. meningitidis). Children with a moderate form of selective IgG deficiencies are advisable prophylactic courses of antibiotic therapy, and with severe form-intravenous immunoglobulin.

5. Hyper-IgM syndrome. The basis of the pathology in this case is a violation of the expression on the T-cells of the molecule CD154 (CD40L), which is a ligand of the CD40 receptor on the surface of B cells. As a result, a signal responsible, in particular, for switching immunoglobulin isotypes is not transmitted to the B cell, and only IgM antibodies are formed. In this disease, the function of T cells that do not receive signals of the opposite direction is also defective due to the absence of the CD40L molecule. Formally located in the group of immunodeficiencies of the humoral unit, hyper-IgM-syndrome is actually a consequence of violations of the T-cell link of the immune system. Persons with hyper-IgM syndrome are prone to frequent recurrent diseases of the respiratory tract, tonsillitis, sinusitis, otitis. A number of people have a tendency to develop opportunistic infections (for example, pneumonia caused by Pneumocystis carinii). It is known that normally this pathogen is effectively eliminated from the body by macrophages receiving the CD40-mediated activation signal from the T-cells side.

B. Secondary immunodeficiency of the humoral link

Reduction of the level of immunoglobulins of different classes can be due to their losses through the gastrointestinal and / or urogenital tracts. For example, in persons with nephrotic syndrome, due to increased filtration in urine, a significant increase in IgA and IgG levels is observed. The serum IgM content is not changed, because of its large size, preventing the passage of IgM glomerular membrane.

2. Immunodeficiencies due to insufficiency of the cellular system of the immune system

As a rule, insufficiency of the cellular part of the immune system has more severe consequences in comparison with the inferiority of the functioning of the humoral link. Most of the genetically caused disorders of the cellular system of the immune system have a poor progosis.

Persons with disorders of the cellular system of the immune system are susceptible to diseases caused by intracellular pathogens (bacteria, viruses), protozoa and fungi. Opportunistic infections are common. In persons with this pathology, hyperergic reactions are almost never observed, most skin tests with allergens, including Candida fungi, as well as tuberculin test are negative, due to pronounced T-lymphocyte anergy.

A. Primary cellular immunodeficiency

Di Georgi syndrome is characterized by pronounced impairment of T-Lymphocyte differentiation due to thymus epithelial dysgenesis and its hypoplasia due to a defect of 3-4 gill arches. As a result, the thymus is not populated by lymphoid precursors and T-Lymphocyte does not develop. The defect of the T-cell link of the immune system is also combined with developmental defects of histogenetically related organs (parathyroid gland, heart and vessels), which leads to cardiac pathology, hypoparathyroidism and severe hypocalcemia.

Adenosine deaminase (ADA) and purine nucleotide phosphorylase (PNP) deficiency. ADA catalyze the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively, and PNP is the conversion of deoxyguanosine and guanosine to guanine, as well as inosine and deoxyinosine into hypoxanthine. The basis of the pathogenesis of these conditions is poisoning by purine metabolites resulting in a steady decrease in immunocompetent cells. In the absence of ADA, deoxyadenosine, adenosine, deoxy ATP and cAMP are accumulated (the first one is the most toxic), which leads to the death of both T and B cells, especially developing developing thymocytes. With deficiency of PNP, deoxyguanosine, GTP and deoxy GTP accumulate, toxic only for T-series lymphocytes.

The "bare lymphocyte" syndrome is an autosomal recessive disease that is a consequence of a violation of the formation of transcription factors (CIITA, RFX-S, etc.), which leads to the absence of expression of all histocompatibility (MHC) genes of classes I and II on the surface of T-and B-lymphocytes and antigen-presenting cells (macrophages, dendritic cells). As a result, positive selection of CD4 + cells can not be performed, and this population is not formed.

B. Secondary immunodeficiency of the cell link can occur as a result of the following causes:

Virus infections (viruses of measles, herpes, human immunodeficiency, cytomegalovirus, etc.). Deficiency of the cellular part of the immune system is caused both by the cytopathogenic effect of viruses and by the hyperactivation of cells, leading to their death by the mechanism of apoptosis (characteristic of HIV infection).

Mycobacterial and protozoal infections lead to immunodeficiency of the cell link as a result of damage to cells of the immune system by microbes and toxins, which causes anergy and death of T cells, as well as activation of macrophage suppressor factors.

Suppression of the cellular system of the immune system in uremia is due to the presence of toxic metabolites and developing acidosis, which causes lymphopenia, by activating suppressor effects in relation to maturation and differentiation of different populations of Lymphocyte.

Suppression of the cellular part of the immune system in case of burn disease is caused by toxic factors and the formation of autoantibodies, which contributes to suppression of phagocytosis, deficiency and suppression of CD4 + T-LYMPHOCYTE functions and hyperactivation of B-
LYMPHOCYTE.

Tumors cause immunodeficiency of the cell link also through toxic and immunosuppressive factors leading to T-LYMPHOCYTE hypofunction, development of blocking effects of antibodies and activation of the suppressor link of the immune system.

Immunodeficiencies due to combined defects of the cellular and humoral parts of the immune system

A. Primary

Single and / or multiple mutations of the genes responsible for the development of the immune response (receptors of lymphocytes, main complexion antigens, adhesion, cytokine synthesis, etc.) can lead to combined immunodeficiency of the cellular and humoral parts of the immune system.

vere combined immunodeficiency (TCID). There are 2 variants of inheritance of
TCID:

A) linked to the X chromosome (about 50% of cases). The basis of pathogenesis is mutations of genes encoding the general g chain of receptors of cytokines (IL-2, 7, 15, etc.), necessary for differentiation and maturation of T and B-lymphocyte. Mutations are recessive, so the pathology is manifested only in men and women heterozygous for this indication. The onset of manifestations is already in the first 3 months of life. Characterized by: pertussis-like cough, korepodobnoj a rash, not giving in to treatment by a diarrhea, visceral candidiasis. Coripiform rash is associated with a reaction of incompatibility to the maternal lymphocytes that enter the bloodstream of the child

through the placenta. The clinical picture is also characterized by a delay in weight gain up to grade II - III hypotrophy, anxiety, anorexia, high sensitivity to infections, including opportunistic pathogens; Pneumocystis pneumonia, malabsorption, progressive encephalitis, generalization in vaccination with live vaccines. The generalization of the infectious process (viruses, bacteria, fungi, protozoa, live vaccine strains) leads to the death of the child. In the septic process, deterioration of the condition and death of the child can occur within 24 hours. . Laboratory indicators - extremely low values of T-Lymphocyte and NK cells and an elevated level of B-LYMPHOCYTE. However, B-LYMPHOCYTE is not able to produce antibodies due to the lack of intercellular interactions between T and B-LYMPHOCYTE.

B) autosomal recessive. About half of the cases are the cause of adenosine deaminase deficiency, which leads to the formation of metabolites of purine bases, toxic to immunocompetent cells (see above). Laboratory indicators - lymphopenia is even more pronounced (in comparison with the previous type of inheritance), the number of T and B-LYMPHOCYTE <500 mm3. The number of NK cells is also reduced, but their function is preserved. The characteristic clinical signs (in addition to those indicated in a) are various deformations of the skeleton, in particular the chest.

The prognosis for all variants of TCID is unfavorable - death occurs either in the first months or in the first 2 years of life. Treatment is not very effective and is directed, first of all, to arresting the infectious process (antibacterial therapy, detoxification, immunoglobulin replacement therapy, etc.). The greatest hope for TCID is associated with transplantation of bone marrow purified from T-lymphocytes in combination with immunoglobulin replacement therapy. Promising methods of treatment of these conditions are bone marrow transplantation and gene therapy (for the first version of TCID) and enzyme replacement therapy (for the second version of TCID).

Combined immunodeficiency (CID)

A distinctive feature is the higher (in comparison with TCID) values of T-Lymphocyte, as well as low levels of antibodies (in the case of TCID antibodies are practically absent). There are 2 variants of CID

- Wiskott-Aldrich Syndrome. It occurs in boys. The pathogenetic basis is a violation of the structure of cell membranes of lymphocytes, processes of tromocytogenesis, IgM deficiency, IgE excess. This immunodeficiency reveals a specific protein WASP (Wiscott-Aldrich syndrome protein), which is associated with a violation of the transmission of intercellular signals and the lack of response to thymus-dependent antigens. The disease begins in early childhood, sometimes in the newborn period with petechiae, ecchymosis, bleeding from the mucous membranes (similar to thrombocytopenic purpura), then the persistent recurrent eczema and infectious syndrome (purulent otitis, pyoderma, pneumonia, colitis) necessarily join. It is characteristic to join allergic diseases (more often atopic dermatitis), lagging physical development up to dystrophy, multiple abscesses. Hemorrhagic syndrome often leads to a lethal outcome (intestinal bleeding, cerebral hemorrhage, parenchymal organs). With cerebral bleeding - paralysis, neurological symptoms. This syndrome is characterized by a tendency to lymphoproliferative diseases. In a laboratory study, the most characteristic is thrombocytopenia with impaired platelet characteristics, low IgM level, a sharp increase (sometimes hundreds of times) of IgE, an increase in IgA and IgD, a normal IgG content, a progressive decrease in T-lymphocytes and an increase in B cells, a decrease in the specific response to Polysaccharide antigens, which makes individuals with this pathology susceptible to infections caused by encapsulated bacteria. Complications often occur in the form of septicemia

30%) and meningitis. The outlook is unfavorable. In severe cases, death occurs in the first 10 years of life. In less severe cases, life expectancy is longer, since dysfunction of T cells at the early stages of development is less pronounced. Nevertheless, it is characterized by a steady tendency towards progression, which is clinically manifested in the tendency to develop malignant neoplasms of the lymphatic system (lymphogranulomatosis, leukemia). Treatment: replacement therapy with immunoglobulins, thymus preparations, correction of hemorrhagic syndrome, antibacterial

therapy. Chicken pox often ends in a fatal outcome. Bone marrow transplantation is considered to be a promising method of treatment. If this procedure is not possible, splenectomy is advisable to prevent a steady decline in platelets and the development of a hemorrhagic syndrome.

Ataxia-telangiectasia (Louis-Bar syndrome) - There is no explicit sexual benefit. The disease begins at the age of 2 - 3 years and later. Pathogenetic basis is loss of cerebellar function (death of Purkinje cells), subcortical ganglia, diencephalic cortex of the hemispheres, hypoplasia of the thymus, lymph nodes, spleen; Deficiency of IgA, cellular immunity. The disease begins with a disorder of gait and balance, often in combination with hyperkinesis, symptoms of parkinsonism, slowing down of voluntary movements, progressive dementia. Such patients are often diagnosed with cerebral palsy or Friedreich ataxia. A significant difference between the Louis-Bar syndrome and these diseases is the appearance, either simultaneously with neurological symptoms, or soon after it, of characteristic changes in the skin and vessels (telangiectasias): a freckle-like rash on the face, whose color resembles "coffee with milk", a characteristic "butterfly" on the face After exposure to the sun, vitiligo and hyperpigmentation; Telangiectasia on conjunctiva of the eyeball, more in the zone close to the eyelids. Teleangiectasias are associated with IgA deficiency. Neurological symptoms and vascular disorders are the main clinical markers, which determine the name of the syndrome (ataxia - telangiectasia). Against this background, the development of severe recurrent and sluggish infections is typical: pneumonia, sinusitis, sinusitis, etc. Pneumonia usually leads to a decrease in the function of external respiration, the development of atelectasis, bronchiectasis, pneumosclerosis. Characteristic for the syndrome of Louis-Bar is a high predisposition to oncopathology and sensitivity to radiation. At laboratory research absence or sharp depression of IgA, depression of IgG2, IgG4, IgE is defined; Decrease in the number of lymphocytes and their response to stimulation of PHA. The prognosis is unfavorable: at an early age, death comes from the generalization of infectious processes; In the distant period - from malignant neoplasms. At the same time, cases of surviving patients up to 40-50 years are described. The treatment is similar to that described in TCID.

B. Secondary

1. Chronic non-specific lung diseases can cause combined immunodeficiency (mainly humoral) due to the polyclonal activation of immunocompetent cells and the enhancement of suppressor factors as a result of prolonged action of inflammatory factors and toxins.

2. Deficiency of microelements causes combined immunodeficiency (mainly cellular) due to the disturbance of signaling pathways involved in gene reanimation, protein activation and contributing to the formation of different populations of Lymphocyte. For example, a deficiency of Zn can lead to defects in the development of T cells, a decrease in the activity of T and NK cells, and neutrophils. Deficiency of Cu - hypofunction of T-cells, defects of phagocytosis.

3. Fasting leads to total (mainly cellular) immunodeficiency due to lymphopenia and hypofunction of immunocompetent cells as a result of protein deficiency and energy supply disorders of cells.

4. Chemotherapy and irradiation lead to combined immunodeficiency due to cytotoxic effects on immunocompetent cells, induction of their apoptosis or necrosis, and suppression of lympho-and myelopoiesis.

13. Immunodeficiencies due to insufficiency and weakening of the function of proteins of the complement system.

Insufficiency of complement is no more than 2% of all primary immunodeficiencies. Most primary defects of one or more components of the complement system are inherited by an autosomal recessive trait and are manifested by a violation of opsonization, phagocytosis, and destruction of microorganisms.

It is accompanied by severe infections, up to sepsis. Insufficiency of complement is often observed in autoimmune diseases, for example, SLE (systemic lupus erythematosus).

Individuals with a C2 defect component are susceptible to diseases caused by encapsulated bacteria (eg S. pneumoniae).

Persons with a defect in the C3 component are predisposed to infections caused by pyogenic bacteria that activate the complement system through a lectin-mediated and alternative pathway (encapsulated bacteria, S. aureus, etc.), and also due to the opsonization of the phagocytosis object.

Persons with deficiency of the final components of complement activation (C5-C9) and also components of the alternative pathway - factor D and properdin are susceptible to infections caused by two species of Neisseria - N. gonorrhoeae and N. meningitidis. Persons with this pathology are very susceptible to inflammation of the meningitis caused by N. meningitidis. This also indicates that the presence of a membrane-attack complex is extremely important for protection against bacteria that are outside the target cells. This is confirmed by the fact of a 10 000-fold increase in the incidence of meningitis in persons who have genetic defects in the membrane-attack complex.

Since the early components of the complement system (C1q, C1r and C1s, C4 or C2) normally participate in the elimination of immune complexes and cells undergoing apoptotic death, their defect may lead to the development of autoimmune diseases, manifested, for example, in lupus-like syndrome.

The most severe clinical manifestations have a violation of complement functions associated with a deficiency of C1 inhibitor, which leads to hereditary angioedema. The disease is transmitted as an autosomal dominant trait. The inhibitor C1 blocks not only the classical pathway of complement activation, but also inhibits the activity of the elements of the kinin and plasmin system associated with it, as well as the blood coagulation system. The development of angioedema is caused by the accumulation of peptides C5a and C3a, which have a strong vasotropic effect and contribute to an increase in the permeability of capillaries. Accumulation of large fragments participating in the cascade of complement reactions is neutralized due to the active work of the complement control system.

It should be noted that the defect of a number of complement components does not lead to clinical manifestations, as it is overlapped by other components of this system. For example, the defect of components C1 and C4 does not lead to an increase in susceptibility to bacterial infections, since the complement system can also be activated by alternative and lectin-mediated pathways.

Thus, defects in the components of the complement system are accompanied by a decrease in resistance to certain infections (in particular, neisserial) and immunocomplex pathology with lupus syndrome. There is a certain selectivity in the relationship between the breakdown of genes of specific groups of factors and types of disturbances. For example:

4. a decrease in resistance to infection by Neisseria is characteristic for defects in the factors of the alternative complement pathway, as well as late components;
5. immunocomplex lesion is inherent in defects of early factors of the classical pathway;
6. in case of NW deficit all characteristic types of lesions are combined, which reflects the key position of this factor in the complement system.

Attention is drawn to the insignificance of the consequences of the disturbance of the lytic phase of complement activation (resistance only to Neisserias decreases, and genetic defects of factor C9 do not appear clinically at all), which obviously reflects the "modest" significance of the corresponding mechanism in immune defense.

Immunodeficiencies associated with deficiency of phagocytic function *A. Primary*

The majority of abnormalities in this group of diseases is due to the weakening ability to recognize and / or kill extra- and intracellular pathogens.

8 onic granulomatous disease. The predominant type of inheritance is X-linked (80% of patients are males), but there is also an autosomal recessive form of the disease. The basis of pathogenesis is the weakening of the bactericidal properties of neutrophils because of their inability to produce active oxygen species necessary for oxygen-dependent killing of phagocytosed microorganisms. Clinically, the disease manifests itselymphocyte in the form of recurrent infections caused by microorganisms that produce catalase (Staph. Aureus, Serratia, Escherichia, Pseudomonas). Of great etiological significance are different types of Aspergillus, causing pneumonia or disseminated infections, and Candida, which affects predominantly soft tissues. The disease usually begins in early childhood, but occasionally its manifestation is delayed until adolescence. The clinical picture includes delayed physical development, purulent lymphadenitis, hepatosplenomegaly, purulent skin and subcutaneous tissue infections, pneumonia, liver abscesses and hemogram changes indicating chronic infections. There are also rhinitis, dermatitis, diarrhea, perianal abscesses, stomatitis, osteomyelitis, brain abscesses, impaired gastrointestinal tract and genitourinary tract (formation of granulomas). Laboratory diagnostics is based on chemiluminescence and NST tests. The courses of antibiotic therapy and interferon g-therapy

9 Syndrome of "lazy" leukocytes and Schwartzman's syndrome. The basis of the pathogenesis of these conditions is the defects in the genes of membrane adhesion molecules, which leads to marked disturbances in neutrophil chemotaxis and monocytes / macrophages, as well as their interactions with other types of cells. An example is phenotypically similar lesions that develop as a result of hereditary defects in the expression of β2 integrins (their common chain, CD18) and carbohydrate determinants of L (CD15) recognized by selectin L (CD62L).

B. Secondary

Defects of phagocytic function can also be the result of various factors (chemotherapy, immunosuppressants, glucocorticoids, tumors, etc.), the effect of which was considered in the previous sections.

Secondary immunodeficiencies

Secondary immunodeficiency (other than AIDS) is usually a syndrome that complicates the course of the underlying disease or pathological process.

There is no generally accepted classification of secondary immunodeficiencies. Depending on the etiologic factor, the following groups are usually distinguished:

5. Acquired Immunodeficiency Syndrome (AIDS).
6. Infectious diseases: bacterial, viral, parasitic infections.
7. Exogenous effects. Of the exogenous effects, those who are able to inhibit reproduction of rapidly growing lymphoid cells (ionizing radiation, cytostatics, etc.)
8. Stress
9. Diseases of the immunocompetent system: defective B-link (chronic lymphocytic leukemia) or T-link (lymphogranulomatosis).
10. Generalized lesions of the bone marrow (myelosis, myelofibrosis).
11. Metabolic and intoxication disorders: micronutrient deficiency, protein loss, exhaustion, burn, uremia, tumors.
12. Immunodeficiencies in aging.

The most important of the secondary immunodeficiencies is AIDS.

AIDS

Human Immunodeficiency Virus (HIV) - RNA-containing retrovirus.

It is absolutely proven that the surface HIV glycoprotein (gpl20) has a high affinity for the CD4 receptor. This explains the selective damage of the Xz helper virus, as well as other cells, especially macrophages expressing CD4 receptors. Connecting to the receptor, the virus is implanted into the cells. There is a reverse transcription of the genome of the virus, leading to the formation of proviral DNA, which is integrated into the genome of the host cell. RNA and mRNA of the virus are formed, that is, the virus begins to multiply.

The key event in the development of AIDS is the defeat of the CD4 + T-helper virus, leading to the death of these cells. The destruction of T-helpers, which perform the basic regulatory role in triggering the reactions of cellular and humoral specific immunity, as well as nonspecific immunity, violates the formation of an adequate immune response.

Infection with CD4 + virus by monocytes and macrophages does not cause the death of these cells, but leads to important consequences, since infected cells:

- serve as an essential reservoir for HIV;
- transfer the virus to various tissues of the body, especially in nervous tissue.

For AIDS patients it is typical:

- Reduction of resistance to opportunistic infectious agents (fungi of the genus Candida, pneumocysts, etc.), which causes the development of AIDS-specific infectious complications:
- Candidiasis of the mucous membranes, - pneumocystis pneumonia,
- intestinal dysbiosis
- Oppression of antitumor immunity, which is manifested by the development of characteristic tumors:
- Kaposi's sarcoma (from endothelial tissue),
- malignant lymphomas (tumors of lymphoid tissue); - CNS damage, causing neurological disorders.

PRINCIPLES OF THERAPY OF IMMUNODEFICIENCES

General tactics

7. Treatment is determined by the type of immunodeficiency.
8. In severe T-cell pathology, bone marrow transplantation is indicated.
9. With IgG deficiency, intravenous administration of solutions containing Ig.
10. Do not administer live vaccines to immunocompromised patients and their families. When cellular immunodeficiency is contraindicated, transfusion of fresh blood and blood products. Ig and plasma should not be administered to patients with selective IgA deficiency. In thrombocytopenia, intramuscular injections should be avoided. Before the surgical or dental procedures, antibiotics should be prescribed.

Drug therapy

1. Practically for all forms it is necessary to appoint:
8. Antibiotics (for prevention and immediate treatment of infections).
9. Immunostimulants (eg, levamisole, ascorbic acid, to improve the function of neutrophils).
2. For humoral and combined immunodeficiencies - Ig substitution therapy.
3. In case of adenosine deaminase deficiency, substitution therapy with enzyme conjugated with polyethylene glycol (Adagen). Gene therapy (corrected T-lymphocytes of the patient) is also performed.

Complications of immunodeficiencies

8. Autoimmune diseases.
9. Development of serum sickness in treatment with γ-globulin.
10. Development of malignant neoplasms (eg, with hypogammaglobulinemia, thymoma may develop).
11. Severe infections.
12. "Graft versus host" reaction (usually as a result of blood transfusion in patients with severe combined immunodeficiency).

Prevention

At primary immunodeficiencies it is necessary mediko-genetic consultation.

hological tolerance

Immunological tolerance is a condition characterized by the "tolerance" of the immune system in relation to foreign AIs. Immunological tolerance is divided into physiological, pathological and artificial.

Physiological tolerance

Physiological tolerance implies the "tolerance" of the IBN system to its own AG.

The main mechanisms of development of physiological tolerance:

14. Clonally selective
15. Insulation »
16. Elimination of autoaggressive T-lymphocytes in the thymus ("central selection")
17. Anergy of T-lymphocytes not exposed to the action of costimulatory molecules ("clonal anergy")
18. Depression of T-killers by T-suppressors
19. Apoptosis of lymphocytes, activated by endogenous antibodies ("clonal deletion")

8.Elimination in the antenatal period (when the immune system is not yet ripe enough) of those clones of lymphocytes that have undergone antigenic overload - the massive effect of their own hypertension. This position was put forward by M. Bernet and F. Fenner in the clonal-selection hypothesis formulated by them. In the laboratory, this phenomenon is reproduced by replanting the embryo and the fetus of the animal tissue or organ of another animal of the same species (allograft). Repeated transplantation to an adult animal of the same transplant does not lead to its rejection - tolerance develops to it. Such animals (in the body of which there is genetically and antigenically a foreign tissue or organ) are called chimeras. Similar chimerism develops in the twins and twins, which during the prenatal period are exchanged by different blood. In the adult state, they can freely transfuse the blood of both groups.

9. Isolation of AG of a number of organs from contact with immunocytes by structural and physiological barriers. These organs include the brain, eyes, testes, thyroid gland, which are separated from the internal environment of the body by hemato-tissue barriers (hemato-encephalic, hemato-ophthalmic, hemato-thyroid). This kind of tolerance is called insulating.

10. Suppression of proliferation and differentiation of autoaggressive (acting against own cells) T-lymphocytes in the central organ of the immune system - thymus. This phenomenon is called the central selection and elimination of autocytotoxic lymphocytes.

11. Death (apoptosis) of clones of lymphocytes activated by autoantigens. In such a situation, T-lymphocytes, responsive to the AG of their own organism, express Fas-receptors, which are acted upon by Fas ligands of normal cells, which activates the apoptosis program.

Pathological tolerance

In this case, we are talking about the "tolerance" of the system of IBS of foreign AG, most often - bacteria, viruses, parasites, malignant tumor cells or a transplant.

The main mechanisms of pathological tolerance:

9. Immunodeficiency states and immunodeficiencies.

10. Excessive increase in activity of T-suppressors. The latter is characterized by inhibition of the maturation of the effector cells of the immune system: T-killers, natural killers, plasma cells.

11. Inhibition or blockade of cytotoxic reactions of cellular immunity to the corresponding AH (most often tumor cells, grafts or virus-containing cells) as a result of "screening" of antigens with antibodies.

12.Overload of immunocytes by excess of foreign AGs formed in the body or introduced into it from outside. This can be observed in the synthesis of abnormal proteins in the liver, amyloidosis, denaturation of protein molecules with massive burns, the introduction of a large number of protein-containing solutions (whole blood, plasma).

9. Death of cytotoxic T-lymphocytes with the development of T-cell immunodeficiency. This is observed when other cells (eg, tumor cells) express Fas ligands. The latter, interacting with Fas-receptors of cytotoxic T-lymphocytes, activate the program of their apoptosis.

Artificial Tolerance

Induced (artificial, medical) tolerance is reproduced by means of influences that suppress the activity of the immune system. Usually, ionizing radiation, high doses of cytostatics and immunosuppressants are used for this purpose. To create a state of artificial tolerance, special cells (impermeable to immunocytes) implanted under the skin, mucous membrane, into muscles or body cavities are also used. A homogenate or fragments of foreign tissue (for example, the endocrine gland to eliminate the deficiency of endogenous hormone) are placed in the chamber. This kind of tolerance is called insulating.

The state of induced tolerance is used to increase the success of organ and tissue transplantation, allergy treatment, immune auto-aggression diseases, endocrine insufficiency and some other conditions.

The "graft versus host" reaction

The "graft versus host" reaction develops when the donor tissues containing immunocytes (for example, bone marrow, spleen, leukocyte mass) are transplanted to the recipient (the "host"). Conditions for the development of "graft versus host" reactions

- Genetic alienity of the donor and recipient.
- The presence of a large number of lymphocytes in the transplant.
- Inability of the recipient to destroy or reject this transplant.

Manifestations

The "graft versus host" reaction is characterized by the defeat of the immune system of the recipient and the development of immunodeficiency in connection with it. In addition to the immune system, other organs are always damaged: skin, muscles, gastrointestinal tract, liver, kidneys.

The lesions of these organs and tissues are manifested by necrotic and dystrophic changes, the development of deficiency of their functions, lymphopenia, anemia, thrombocytopenia, dyspeptic disorders (nausea, vomiting, diarrhea), liver enlargement.

10. In adults, the described condition is called homologous or transplantation disease.

11. Wound disease develops in children - a small-growth disease (from English, runt, the smallest individual). The latter is associated with a violation of the child's physical development, m to evelop infectious diseases and neoplasms.