Fundamental studies of the response patterns of the human immune system in the conditions of the North

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Abstract. The paper presents the facts and patterns that indicate the differentiation of immune responses to adaptive, regulatory and prenosological influences in response to the adverse effects of climatic and geographical factors. The activation of migration reactions of peripheral blood cells in response to an increase in the concentration of antigens or autoantigens causes hemodynamic reactions with the release of hemopoietic cells to the periphery of the depot, urgent catecholamine reactions and prolongation of them, if necessary, with glucocorticoids. Prenosological signs of the risk of disrupting regulatory mechanisms are neutropenia of lymphopenia, lack of phagocytic protection, an increase in the concentration of pro-inflammatory cytokines and the extracellular pool of receptors due to an increase in their shedding.

1. Introduction
The immune system ensures the constancy of the body’s internal environment by controlling and regulating the level of adoptive reactions. Immunocompetent cells exist in any organ and any tissue; their mediators and cytokines overcome all existing barriers. Therefore, the immune background integrally reflects the state of the mechanisms ensuring and maintaining homeostasis. Protective immune responses are a part of the overall neuro-immune-endocrine regulatory system, providing an adaptive life-supporting response in the specific conditions of the influence of adverse climatic and geographical factors. There is dependence between the formation and manifestation variants of the secondary environmentally dependent immunodeficiency and the period of living and working in the Arctic. The criteria for the risk of failure of the adaptive mechanisms of the immune protection regulation are established, a set of therapeutic and preventive measures has been developed. The fundamental issues of differentiation of adoptive, compensatory and pathophysiological mechanisms of the immune system reactions in the process of human adaptation during work in the arctic conditions have not been resolved. In this paper, an attempt was made to establish the role of hemodynamic changes in the composition of the mechanisms for maintaining homeostasis under conditions of intense immune background.

2. Materials and research methods
The paper summarizes the results of many years of research on the state of the immune status of practically healthy adults aged 25–55 years old, residents of the Nenets Autonomous District, the Murmansk region and the village of Barentsburg on Svalbard archipelago. The survey was conducted in the periods of the polar night and the polar day (January and July). All studies were carried out with the consent of volunteers and in accordance with the requirements of the Helsinki Declaration of the...
World Medical Association on the ethical principles of medical research (2000). In the venous blood, the enzyme immunoassay determined the concentrations of endothelin-1, brain sodium-uretic peptide by its N-terminal fragment Nt-prp-BNP and irisin, cytokines (IL-1β, 4, 6, 10, 13, 17, TNF-α, IFN-γ), as well as by the method of competitive enzyme immunoassay for lymphocyte phenotypes (CD3, 4, 8, 10, 16, 23, 25, 95 and HLADRII). The used test kits were Vector-Best, Russia; BCM Diagnostics from Bio-RAD, CYTIMMUNE sciences INC and CytElisa (USA); «Dr. Fooke» (Germany) and DRG Instruments GmbH (Germany).

3. Research results and discussion

Immune reactions develop as a reaction to nearly any quantitatively significant deviation of the internal environment composition. Recognition of abnormally high concentrations of any metabolic product or exogenous penetrating antigen using pattern-recognizing receptors (PAMPs) has been established in invertebrates [1]. Damage to cells induces the expression of damage receptor genes (DAMPs), which, like PAMPs, also respond to changes in the intercellular environment by cytokine production [2]. In addition to cytokines, the cell secretes a number of mediators, such as retinoic acid, stromal lymphopoietin (TSLP), transforming growth factor (TGF) and IL-10, which provide a normal level of innate immunity reactions involving macrophages, dendritic and mast cells, natural killer cells (NK), natural killer cells of T-origin (NKT), regulatory γδ T-cells, B1-lymphocytes and lymphocytes of innate immunity (ILC) [3 - 5]. The reaction of preventive inflammation is a common, one of the first and phylogenetically early reactions aimed at restoring homeostasis. In the course of its development, the synthesis of proteins of the acute phase, IL-1β, chemokines and transendothelial migration of blood cells occurs [6 - 9]. The chemokine-activated signal complex depends on a set of signal molecules specific for each type of leukocyte [10 - 12]. Later, when they appear in the tissues, the leukocytes move, following the chemokine gradient, to disadvantaged areas. In peripheral blood, there is a decrease in the content of circulating leukocytes, mainly neutrophils and monocytes. The migration of immunocompetent cells constitutes the obligatory and early part of immune reactions, which include, in addition to migration, proliferation, death and regeneration. Migration of granulocytes and monocytes to the place of influence of the antigen (pathogen) with the purpose of its recognition and destruction is one-sided; the migration of lymphocytes can be one-sided and recycle [13 - 17]. Migration duty is fundamental for granulocytes and monocytes; their phagocytic and secretory functions are realized in the tissues and not in the blood (with the exception of blood infections). Migratory activity is provided by histamine, norepinephrine, adrenaline and endothelin-1, the content of which is significantly higher among people living and working in the Arctic [18, 19], as well as cortisol [20, 21].

The activation of migration reactions is manifested by a decrease in the content of leukocytes circulating in the blood. Neutropenia (neutrophil count <2 × 109/l) is common in the North and is registered in 9-21% of adults of working age. The frequency of neutropenia registration is higher in winter (in January, 21.36 ± 1.43; in June, 9.58 ± 0.78%). The duration of neutropenic states in winter is significantly higher than in summer (52.46 ± 16.35 and 26.31 ± 7.36 days respectively). In 88.97%, neutropenic states are transient in nature, manifesting themselves mainly in winter (cases of neutropenia were registered in 1557 of 1750). The relative registration level of permanent neutropenia during the year at the time of the examination 1 per quarter was 8.74% (153 people). In neutropenia, the frequency of registration of neutrophil phagocytic activity deficit (% of phagocytic cells <50) increases dramatically from 32.35 ± 0.21 to 68.74 ± 0.82%, monocytes from 17.42 ± 0.11 to 33.86 ± 0.57 and higher concentrations of interferon-γ and IL-17F. IL-17 stimulates neutrophil infiltration, primarily activating migratory ability [22]. IFNγ increases the efficiency of antibody-dependent cytotoxicity of neutrophils and eosinophils through the expression of high-affinity FeγR (CD64) genes [23 - 26]. Neutropenias in healthy people can occur with increased physical exertion, chills, neurotic states, immediately after hemodialysis, with tissue hypoxia, anemia and parasympathicotonia, as well as during the first hours after vaccination, with infection with respiratory viruses, with some bacterial infections [27, 28]. Neutrophil deficiency is associated with an increase in
peripheral blood levels within the regulatory limits of histamine and catecholamines, including dopamine, norepinephrine and adrenaline (p = 0.03-0.01).

The decrease in the content of cells circulating in the blood serves as the main signal for complex multicomponent reactions for maintaining the constancy of the cell circulating pool. The most urgent is the entry into the circulation of cells from the depot: neutrophils - mainly from the capillary network of the lungs; lymphocytes - from lymphoid organs [29 - 33]. The tissue pool of monocytes is 3.5 times higher than the content of tissue neutrophils [34], so the migration processes of monocytes from the blood may seem less intense and less pronounced. In fact, any irritation that requires an increase in the oxygen capacity of the blood, involving the secretion of catecholamines into protective processes, causes the release of blood from the depot. Blood is deposited in the lungs, spleen, liver, and subcapillary venousplexuses of the skin [35, 36].

Lymphoid organs are open with a constant influx of cells from the outside and exit into the circulation. With increasing activity of migration and hemocirculation in the blood, as a rule, the content of small lymphocytes increases, and in their composition appear stem cells. Lymphopenia (the content of lymphocytes in the blood is less than 1.5 × 10⁹/l) is recorded on the first day of an acute inflammatory process, traumatic illness, and acute blood loss [37 - 43]. The movement of lymphoid cells is of particular importance, because this process occurs not only within any organ of the lymphoid system, but also between individual lymphoid organs, as well as during the migration of lymphocytes to organs of other systems [44 - 50]. With an increase in the activity of migration and hemocirculation in the blood, as a rule, the content of small lymphocytes increases, and in their composition appear stem cells. Asymptomatic lymphopenias are not so very rare among residents of extreme climatic zones and are associated with an increase in the amplitude of oscillations of the magnetic field. In the Arkhangelsk region, October and November are the most anomalous months, when the variations are of a sharply disturbed nature (up to 300 nT in 15 min), as well as the first two weeks of March (maximum amplitude of 320 nT). On average, the frequency of lymphopenia registration in adults of working age is 19.86 ± 0.54%. On magnetically disturbed days, the total lymphocyte amount in venous blood decreases due to mature CD3 + T cells and activated CD71+, CD25+ and HLADRII lymphocytes, as well as natural killer cells [51, 52]. During magnetic disturbances, blood viscosity increases in arteries, blood flow in capillaries slows down, platelet aggregation changes, leukocyte ratio changes [53 - 56]. At high latitudes, the amplitude of oscillations of the magnetic field is 2-3.5 times greater than in the middle zone of the Russian Federation due to the peculiarities of the structure of the magnetosphere. The anomalous course of variations up to 20% of the amplitude change is established within a 10-kilometer zone on both sides of the coastline of the Arctic Ocean. The decrease in the functional activity of the cell under conditions of anomalous variations in the earth’s magnetic field is associated with conformational changes in the cell's receptor zones and a decrease in the activity of signal transmission through any receptors and especially the Ig Fc receptors [57, 58].

One of the main mechanisms of cell activity regulation is the change in the number of different receptors on the cell membrane. We have previously shown that northerners have lower blood levels of mature T-lymphocytes with the CD3 receptor, cells with activation receptors (for interleukin-2, transferrin and antigens of the main histocompatibility complex HLADRII). Shedding or proteolytic cleavage of the extracellular part of membrane receptors from the surface of any cell, including immunocompetent, has a significant impact on the levels and development of immune responses. The inhabitants of the polar regions have higher blood concentrations of free receptors for transferrin sCD71 (700.2 ± 50 and 2070.5 ± 140 ng / ml) and transferrin itself (239.81 ± 19.99 and 263.40 ± 1.78 mg / d) against the background of almost equal levels of serum iron (17.38 ± 0.85 and 18.02 ± 0.89 μmol / l) and cells (CD71+) with a receptor for transferrin (0.47 ± 0.03 and 0, 45 ± 0.02 × 10⁹ cells / l). In the presence of active phagocytes deficiency, healthy receptors in the blood plasma are significantly (2-3.5 times) higher than in the territories of a more favorable climate. This applies to virtually all of the studied receptors and lymphocyte differentiation clusters, including those involved in activation, differentiation, migration, cooperation, and antibody-dependent cytotoxicity. It has been
proven that receptors shedding is increased with an increase in the concentration of cells in the blood with the corresponding membrane forms and, in essence, regulates the functional activity of the cell, reducing the number of receptors on the membrane. Extracellular receptors retain the ability to respond with the appropriate substrate, which ensures their binding (neutralization, deposition, utilization and subsequent excretion from the body). A significant increase in the extracellular pool of biologically active receptor structures has a significant inhibitory effect on the activity, efficiency of cell-mediated, antibody-dependent immune responses.

Changes in the ratio of the depot of blood cells and circulating pool is the main signal for a wide range of changes in total hemodynamics: reorganization of the microvascular bed with an increase in the tone of precapillary arterioles and a decrease in the activity of venous blood discharge, an increase in the linear blood flow velocity. The earliest processes of regulation of the state of the microcirculatory bed are endothelial reactions. The phase of absorption of the extracellular medium forms a cycle of nitric oxide NO-NO2-NO3-NO; in the absence of nitric oxide secretion (absence of absorption), the endothelium cell constantly secretes endothelin vasoconstrictor. It was established that the decrease in the content of circulating cells depends on the initial concentration of endothelin-1: in individuals with a high initial level of this peptide in plasma (1.56 ± 0.39 fmol / ml) a decrease in their concentration is expressed; low concentrations of endothelin-1 (0.32 ± 0.04 fmol / ml) are associated with lack of response from leukocytes. The action of endothelin - vasoconstrictor - determines the parameters of cell perfusion in the distal volume of the arterial bed, and prolonged absence of vasodilation disrupts microcirculation and forms a violation of metabolism. Increasing the hydrodynamic pressure above the membrane increases filtration and can lead to a loss of the intercellular fluid pool. In order to prevent this, the effect of angiotensin II, which causes a spasm of afferent arteries, is activated, bringing active filtration in line with the possibilities of passive diffusion. Aldosterone ensures the preservation of sodium in the extracellular medium, and BNP initiates the secretion of sodium against a density gradient. In these situations, there is a danger of a change in hydrodynamic pressure, which is prevented by the reaction of an increase in the blood content of the brain sodium uretic peptide (brain natriuretic peptid - BNP). An increase in blood pressure, stroke and minute volumes of the heart can lead to an increase in hydrodynamic pressure in various parts of the circulatory system. Increasing the hydrodynamic pressure above the membrane increases filtration and can lead to a loss of the intercellular fluid pool. In order to prevent this, the effect of angiotensin II, which causes a spasm of afferent arteries, is activated, bringing active filtration in line with the possibilities of passive diffusion. Aldosterone ensures the preservation of sodium in the extracellular medium, and BNP initiates the secretion of sodium against a density gradient. The interrelation of increasing the content of BNP in the blood serum and reducing the activity of the reactions of preventive inflammation and adoptive immunity is indirect; it is determined by the need to provide urgent and long-term reactions of constant hydrodynamic pressure and volume of intercellular water.

Glucocorticoids prolong urgent adaptive reactions induced by catecholamines and other vasomotor amines, mobilize plastic functions, creating a foundation of free amino acids in favor of the formation of fats and carbohydrates, and prevent the development of excessive tissue reactions by inhibiting the secretion of hormones [59 - 61]. The intensification of catabolism processes during long-term adaptive reactions against the background of high concentrations of cortisol sooner or later leads to a reduction in reserves for the regulation of homeostasis, up to exhaustion. In these cases, the content of catecholamines, unlike cortisol, does not decrease even when the stressful situation becomes habitual [62 - 64]. This situation is associated with the formation of uncompensated T-helper immunodeficiency.

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