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## EDITOR'S COLUMN



*Dear Colleagues!*

We are summing up the outgoing 2018 on the threshold of the upcoming 2019. For the Yakut Medical Journal, the year was prosperous and fruitful: we have celebrated the 15th anniversary of the journal; the journal is included in the international citation database Web of Science in test mode; the journal's demand for authors and readers from different regions of Russia, including Yakutia, has significantly increased.

We are representatives of the most humane profession - the profession of a doctor. And our activity is entirely focused on improving and preserving the health of people, increasing the lifespan and improving the quality of their life. Many scientific developments of the YSC CMP have global and practical significance. This is what stimulates us to work, to overcome, and sometimes to exploits that are not always noticeable to the others, but this does not diminish their significance.

A strong fundamental and applied science, combined with practical developments, new technologies, quick response to innovation is the visiting card of the YSC CMP. On the pages of our Journal you will find a confirmation of this statement.

Thanks to sustainable financing and professional work of the editorial board, the Yakut Medical Journal has successfully passed the stage of formation and has sufficient potential for further sustainable development. Work on improving the quality of published materials will continue, which implies an improvement in the pre-production work (collection, review of the material, work

with authors, etc.). The main headings of the journal will remain the same. At the same time, the priorities are "Original research", "Methods of diagnosis and treatment", "Arctic medicine", "Scientific reviews and lectures", "Hot topic", etc. Special attention will be paid to headings that publish practical medicine materials.

We will continue work on improving the site of our journal. The editorial board will contribute to a steady feedback from the users of the Yakut Medical Journal in order to improve the quality of the journal in every way, increase of its competitiveness, informativeness and accessibility. The editorial board works with authors with great inspiration and does everything so that readers can get acquainted with the interesting results of scientific research in the pages of our journal. We are ready to listen to your opinion about the magazine and take good suggestions for its improvement.

On the eve of the New Year, I wish our dear authors and readers good health and high spirit, new great ideas and achievements! May the New Year be successful and productive for all of us! Well-being and happiness!

*Director of the YSC CMP, MD A.N. Romanova*



## ORIGINAL RESEARCHES

A.T. Diakonova, N.I. Pavlova, N.A. Solovyeva,  
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## MOLECULAR-GENETIC ANALYSIS OF THE CONNECTION OF THE SLC6A3 GENE WITH NICOTINE ADDICTION IN YAKUTIA

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### ABSTRACT

The purpose of this work is to study the relationship of the gene *SLC6A3* rs27072 with nicotine addiction in the smoking population living in Yakutia. In total, we examined 100 people (men and women aged 20 to 70 years). The status of smoking was revealed at the questionnaire. Smoking cigarettes, like many other addictives, has a genetic component. The *SLC6A3* gene is an important candidate for predisposition to nicotine addiction. Analysis of the polymorphism association of *SLC6A3* rs27072 with nicotine addiction testified the absence of statistically significant differences between carriers of different genotypes, not only in the study group as a whole, but also separately in men and women. Probably, this is due to the small sampling and difficulties in determining the status of smoking using only questionnaires.

**Keywords:** smoking, nicotine addiction, *SLC6A3* gene, Yakutia, polymorphism.

**Introduction.** Cigarette smoking remains widespread, a risk factor for more than two dozen diseases and is the biggest cause of death all over the world. Smoking damages virtually all systems of the human body and is a habit that can be got rid of. Smoking of tobacco causes psychological and physiological addiction and, in addition, is closely related to social and cultural factors. Despite widely recognized risks, about one third of the world's adult population continues to smoke tobacco [1].

According to the World Health Organization (WHO), smoking causes nearly 6 million deaths each year, of which more than five million occur among smokers. The Fig. 1 shows the prevalence of smoking in the world. Smoking prevalence is prevalent in Asian countries [2].

Also among non-smoking people, more than 600,000 are exposed to second-hand tobacco smoke. WHO estimates that tobacco contains more than 7,000 chemical compounds, 60 of which are known or suspected carcinogens, i.e. cause changes in the cells of the body leading to the development of cancer, and 250 have a proven cytotoxic effect. Eleven substances contained in tobacco smoke (2-naphthylamine, 4-aminobiphenyl, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium, cadmium and polonium-210), the International Agency for Research on Cancer refers to the first group of carcinogens (ie with a proven carcinogenic effect) [2].

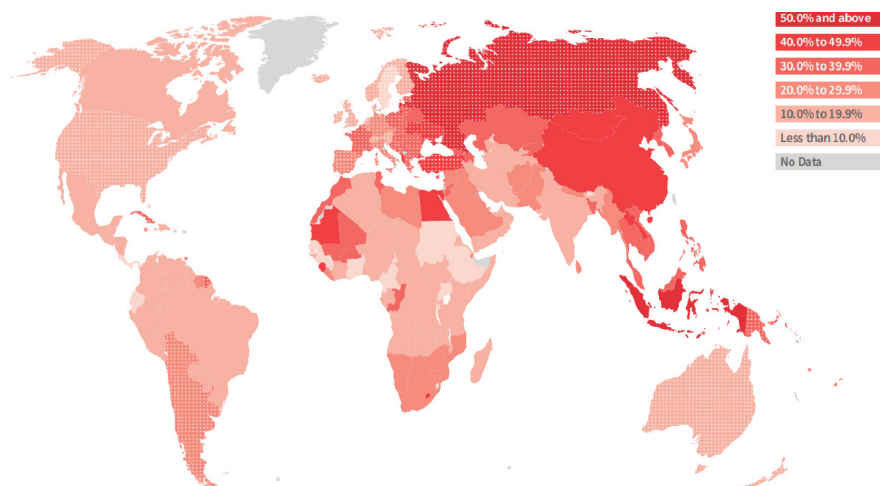
It is assumed that there is a central pathophysiological mechanism for maintaining addiction on psychoactive substances, under genetic control. This mechanism is independent of the specific type of psychoactive substance

and causes neurochemical changes in the future patient even before the meeting with psychoactive substances, and this includes nicotine addiction. Which determines the biological basis of the predisposition proper. However, the conclusions between previous studies are difficult to explain because smoking cigarettes is a very complex process, influenced by various factors such as age, sex, environment [1].

The dopamine transporter gene (*SLC6A3*) localized in the short arm of chromosome 5 (5p15.3) participates in the control of dopaminergic transmission. The rs27072 polymorphism of the *SLC6A3* gene is associated with more severe symptoms with an alcohol withdrawal syndrome, such as convulsions. Many authors report that the gene of the dopamine transporter (*SLC6A3*) is associated with the syndrome of hyperactivity and attention deficit disorder (ADHD). A link was also found between the trans-

porter gene of dopamine and the age of onset with regard to the use of tobacco and alcohol. Studies conducted predominantly in the European population have revealed that the allele of this polymorphism increases the risk of smoking, while studies in the Japanese population have shown a link between this genotype and smoking. Previously, the influence of polymorphisms on ethnicity was also considered. In association studies between the variant *ANKK1 / DRD2* and *SLC6A3* alleles and smoking, it was suggested that the presence of the *ANKK1 / DRD2* Taq I allele along with the A *SLC6A3* allele increases the craving for cigarettes, causing addiction. In addition, several studies have suggested that, compared to non-carriers, carriers of the A *SLC6A3* allele have a lower risk with early onset of smoking [3, 4, 6].

The results of population studies in different countries are presented in Table 1. In the world, the frequency of allele A



**Fig.1.** Prevalence of tobacco smoking in the world: light to dark shows the increase in the percentage of smoking population by country (WHO data on trends in tobacco prevalence, 2015)

was 21%. Studies were conducted in the Chinese population of Han (South China) in which the percentage of allele A was 31%. Also in the Chinese population of Dai (China) was A - 31%, which is the highest rate in the world. In the population of African descent (South-West USA), the lowest A is 10%. In the Yoruba population (Nigeria), the percentage of allele A was 13%, which is also one of the least.

The authors who studied the *SLC6A3* gene relationship with the nicotinic addiction insisted that it had an effect on smoking cessation [4, 8].

The **purpose** of this work was to study the relationship of the gene *SLC6A3* rs27072 with nicotine addiction in the smoking population living in Yakutia.

**Materials and methods of the research.** The experimental part of the genotyping of polymorphism rs27072 of the *SLC6A3* gene was carried out in the laboratory of hereditary pathology of the department of molecular genetics of the Yakutsk Scientific Center of Complex Medical Problems. DNA samples from the YMC KMB biomaterial collection were used for the study using the UMU "Genome of Yakutia" (registration #USU\_507512). The study involved residents of the Republic of Sakha (Yakutia). The study was conducted with the written consent of the participants. A total of 97 DNA samples, 45 males and 52 females, were examined.

Genomic DNA was extracted from the peripheral blood of each participant using the Excell Biotech DNA Excellence Kit (Russia) in accordance with the manufacturer's instructions. The DNA concentration in each sample was determined on an Implen Nano Photometer (Germany) spectrophotometer for measurement in microvolumes. Single nucleotide polymorphisms (SNP) were determined by polymerase chain reaction (PCR-RFLP). Amplification of the region of a gene containing a polymorphic variant was carried out by standard pairs of primers produced by Biotech-Industriya LLC, Moscow. Reaction mixture primer direct and reverse 1 µl; Dream Taq PCR master mix -12.5 µL; 9.5 µl of desionized water and 1 µl of DNA. The total volume of the reaction mixture for amplification was 25 µl. The restriction mixture was 20 µl, 7 µl of amplification, 10.9 µl of desionized water, 2 µl of restriction buffer, and 0.1 µl of restriction endonuclease MspI.

The temperature-time mode for conducting PCR is optimized to amplify this nucleotide sequence and is presented in Table 2.

The detection of PCR products was

Table 1

Frequency distribution of allele polymorphism rs27072 gene *SLC6A3*

Allele	Population				
	All	Southern Han Chinese, China	Chinese Dai, China	African in Southwest, US	Yorubain Ibadan,
Allele A (%)	Nigeria	31	31	10	13
Allele G (%)	79	69	69	90	87

Table 2

PCR conditions

Gene	Amplificate	PCR conditions
<i>SLC6A3</i>	217 п.н.	1. 95°C – 5 min 2. (94°C – 30 sec; 62°C – 30 sec; 72°C – 1 min)-35 cycles 3. 72°C – 7 min

carried out by horizontal electrophoresis in a 2% agarose gel plate with the addition of ethidium bromide-a specific intercalating fluorescent DNA (RNA) dye-using a standard tris-acetate buffer at a field strength of ~ 20 V / cm for 30 minutes.

After PCR amplification was subjected to restriction with the use of endonuclease Msp I (OOO SibEnzim, Novosibirsk) for 3 hours at 37 ° C. The detection of RFLP products was carried out by horizontal electrophoresis in a plate of 4% agarose gel with the addition of ethidium bromide using standard tris-acetate buffer at a field strength of ~ 20 V / cm for 45 minutes (Figure 2)

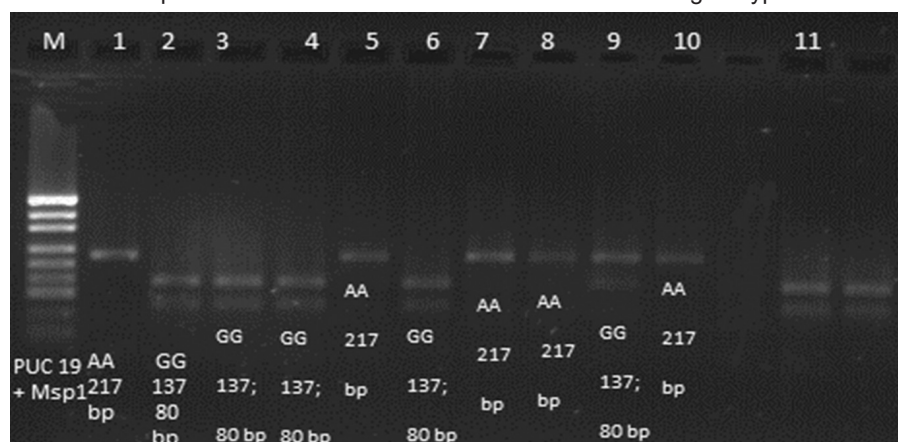
Interpretation of genotyping results was performed on the basis of different band patterns: GG genotype 137, 80 bp, AG genotype 217, 137 and 80 bp, AA genotype 217 bp.

Statistical analysis of the results of the research was carried out using the program: "Office Microsoft Excel 2010". The correlation of the genotype distributions with the expected values at the Hardy-Weinberg equilibrium and the comparison of the frequencies of the allelic vari-

ants / genotypes was carried out using the Pearson method for the 2x2 conjugacy tables, OR, 95% confidence interval (95% CI) . Differences were considered reliable at P <0.05.

**Results and discussion.** As a result of genotyping polymorphism rs27072 of the *SLC6A3* gene, it was established that the incidence rate of the GG genotype among all the examined individuals is 69.1%. The allele frequency G was 80.9% (Table 3).

In our sample, smoking frequency of allele A was 17, 34%, in the non-smoking sample- 20, 83%. Also, with the gender division in the groups of smokers (women) and non-smokers (men), the frequency of allele A was 8.7%, and in the groups not smoking (women) and smoking (men) - 22.4%. The results of the association evaluation of rs27072 polymorphism of the *SLC6A3* gene showed that the incidence of the A allele in the sample of smokers and non-smokers is not significantly different. However, in the sample of smokers, the number of carriers of the homozygous AA genotype exceeded the number with such a genotype in the non-



**Fig.2.** The electrophoregram of the amplification product of the region of the *SLC6A3* gene in a 4% agarose gel: tracks number 1, 5, 7, 8, 10, - genotype AA; № 2, 3, 4, 6 and 9 - genotype of GG; M - marker PUC19 / + Msp I, Bp - base pairs.



Table 3

**Frequency distribution of alleles and genotypes of rs27072 polymorphism of the *SLC6A3* gene**

Comparable groups	Frequency of occurrence of genotypes, abs. (%)			Frequency of occurrence of alleles, %		OR (95% CI), P	p
	AA	AG	GG	A	G	Allele of risk A	
Smoking	5 (10.2)	7 (14.28)	37 (75.51)	17 (17.34)	81 (82.65)	1.247 (0.389-1.636)	0.537
Do not smoke	2 (4.16)	16 (33.33)	30 (62.5)	20 (20.83)	76 (79.16)		
Smoking Women	1 (4.4)	2 (8.7)	20 (86.9)	4 (8.7)	42 (91.3)	0.991 (0.100-1.091)	0.061
Do not smoke Women	1 (3.5)	11 (37.9)	17 (58.6)	13 (22.4)	45 (77.6)		
Smoking Men	4 (13.8)	5 (17.3)	20 (68.9)	13 (22.42)	45 (77.58)	9.125 (0.916-10.041)	0.061
Do not smoke Men	1 (4.34)	2 (8.69)	20 (86.95)	4 (8.7)	42 (91.3)		

smoking sample by a factor of two. Allele in smokers A allele reaches 17.3%, which is almost the same as the percentage of allele A in the sample of non-smokers. The analysis of statistical data between samples of men and women showed similar results in the two groups. This is most likely due to the fact that at a small sample it is necessary carefully refine the unreliability of the detection of smoking in the survey, adding aspects such as length, the number of cigarettes smoked.

Analysis of the association of *SLC6A3* rs27072 polymorphism with nicotine addiction indicated that there was no statistically significant difference between carriers of different genotypes, not only in the study group as a whole, but also separately in men and women (Table 3).

**The conclusion.** The results of a study of polymorphism in the smoking population among residents of the Republic of Sakha (Yakutia) found that among the surveyed persons prevalence was 81% among smokers and in non-smoking 76% of the G. allele, which is not associated with nicotine addiction. In the sample of smokers, the number of carriers of the homozygous AA genotype exceeded the number with such a genotype in the non-smoking sample by a factor of two. But on the whole, according to the statistical data, it turned out that the reliability of the samples was not found.

Thus, as a result of this study, we found that polymorphism rs27072 of the *SLC6A3* gene did not reveal a connection with nicotine addiction in the studied sample. This probably depends on the small sample size and the difficulty in determining smoking using questionnaires. Since we were based only on the honesty of our respondents, in the future, when composing samples, it is necessary to group them according to the age and age of the beginning of smoking.

*The research was carried out within the framework of the R & D study of the genetic structure and cargo of the hereditary pathology of populations of the Republic of Sakha (Yakutia).*

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## EVALUATION OF SUB-POPULATION COMPOSITION OF LYMPHOCYTES IN CHRONIC TOXIC LIVER DISEASE AND ANEMIA OF CHRONIC DISEASE ON THE BACKGROUND OF TRANSMITTED INFILTRATE PULMONARY TUBERCULOSIS

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### ABSTRACT

The article presents the results of the estimation of the subpopulation composition of lymphocytes in 66 patients with chronic toxic liver damage and anemia of a chronic disease on the background of the transferred infiltrative pulmonary tuberculosis. The use of a combination of sirepar and sodium nucleate in the treatment of such patients contributes to the elimination of the clinical phenomena of the combined pathology, and along with the improvement or complete normalization of the clinical indices in the patients examined, normalization of the cellular immunity parameters was noted, which gives grounds for recommendations on the use of the proposed combination of drugs in the complex treatment.

**Keywords:** lymphocytes, cellular immunity, tuberculosis infection, chronic hepatitis, anemia.

**Introduction.** Among infectious diseases, tuberculosis continues to be one of the leading causes of morbidity and mortality among adults throughout the world. Approximately 2 billion people of the world's population are infected with M. Tuberculosis [12]. Every year, almost 10 million people become infected with an active form of tuberculosis and 2 million people die from it [14]. Every 10 seconds from tuberculosis in the world one person dies. So, in the territory of Lugansk region in recent years, due to a number of problems: forced migration, the formation of post-traumatic stress disorder and a decrease in the standard of living of the population, there is an increase in the incidence of tuberculosis. According to statistical data in 2015, the incidence was 58.9 per 100 thousand people, the mortality rate is 12.3 per 100 thousand population, in 2016 these figures were 68.2 and 15.3, in 2017 70.4 and 15.8 per 100.000 of the population, respectively, which exceeds the epidemic threshold.

The need for continued use of antituberculosis drugs led to an increase in the proportion of adverse reactions [11]. The development of adverse reactions to antituberculosis drugs poses a threat to a full-fledged chicken chemotherapy [2, 10]. Interruptions in taking antituberculosis drugs lead to a decrease in the effectiveness of treatment, the formation of tuberculosis with drug resistance, and to an increase in the reservoir of tuberculosis infection [1, 3, 8].

One of the most common hematological disorders in patients with acute or chronic activation of the immune system due to various infectious diseases is anemic syndrome [4, 5]. According to mod-

ern ideas, anemia arising in similar situations is conventionally designated as anemia in chronic diseases (ACH). The frequency of ACH in acute and chronic infections varies from 18 to 95% [13]. ACHs with long-term preservation of the inflammatory process, which is typical for tuberculosis infection, may present difficulties in terms of differential diagnosis with iron deficiency anemia and further treatment.

One of the pathogenetic links of the studied comorbid pathology is the binding of metabolites to hepatocyte proteins with the appearance of autoantigens circulating and fixed on the membranes of hepatocytes, the formation of immune complexes of autoantigen-autoantibodies, and the development of T cell-mediated immunological reactions.

**Purpose of the study:** evaluation of the subpopulation composition of lymphocytes in chronic toxic liver damage (CTLD) and anemia of a chronic disease against a background of transferred infiltrative pulmonary tuberculosis.

### Materials and methods of research.

Under our supervision, there were 66 patients with CTLD, with ACHs on the background of tuberculosis of the lungs, age from 18 to 50 years. The criteria for inclusion in the study were: age from 18 to 50 years, hospital treatment, history of first diagnosed infiltrative pulmonary tuberculosis, chemotherapy under standard regimens using 4 drugs or more, informed consent for participation in the study, the presence of toxic liver damage caused by reception of antituberculous drugs. The criteria for exclusion were: age younger than 18 years and over 50 years, refusal from inpatient treatment, lack of informed

consent, positive ELISA test for the presence of certain markers of viral hepatitis.

All observed patients were divided into two groups: the main group (34 patients) and the comparison group (32 patients), randomized by sex, age, and course of the disease. All patients received standard therapy of hepatitis, including hepatotropic therapy, drugs ursodeoxycholic acid, essential phospholipids, a mixture of amino acids. Patients from the main group were additionally received in a combination of sirepar therapy of 3 ml IV drip in 100 ml of 0.9% fiz. solution and sodium nucleate for 2 capsules (200 mg) 4 times a day for 2 weeks.

The diagnosis of toxic hepatitis was established expertly, taking into account the history, the results of clinical and laboratory (biochemical) research, characterizing the functional state of the liver and gallbladder, as well as data from sonographic examination of the abdominal cavity. To confirm anemia of a chronic disease, hemoglobin (Hb), hematocrit (Ht), reticulocyte count, serum iron level (Fe), total iron binding capacity of serum (TICS) were evaluated.

To achieve the goal of the study, an additional immunological study was performed to analyze the state of the cellular immune system. At the same time, the content of T- (CD3 +) and B-lymphocyte (CD22 +) populations, T helper / induc-tor subsets (CD4 +) and T-suppressor / killer (CD8 +) populations was studied in the peripheral blood using a cytotoxic test using monoclonal antibodies (MBAT). Commercial MCAT classes CD3 +, CD4 +, CD8 +, CD22 + NIC of "Med-BioSpectr" (RF - Moscow) were used in the work. The immunoregulatory index

CD4 / CD8, which was treated as the ratio of lymphocytes with helper and suppressor activity (Th / Ts), was taken into account. Evaluation of immunological shifts of T-cell regulatory subpopulations was performed using the "immunological compass" method, taking into account the relationship between subpopulations of T-helpers and T-suppressors. Functional activity of T-lymphocytes was studied by the reaction of blast transformation of lymphocytes (RTBL) when it was formulated with a micromethod using phytohemagglutinin (PHA) as a nonspecific mitogen.

Statistical processing of the results was carried out according to methods common in experimental medicine using the package of licensed programs Microsoft Excel. The reliability of the differences in the groups was determined by the Student's t-criterion using the Microsoft Excel 5.0 and MedStat software packages [7].

**Results and discussion.** The clinical picture of CTLD and AChs on the background of the transferred infiltrative pulmonary tuberculosis is characterized by the presence of varying degrees of asthenic, astheno-neurotic, moderate cytolytic syndromes, anemia, hepatomegaly, in some patients – cholestatic syndrome, and characteristic changes on the chest radiograph (resorption of infiltrative focal changes in the affected lobes of the lungs, scarring of cavities of decay and compaction of foci).

In the ultrasound study, signs of moderate increase in the liver and an increase in its echogenicity were found in all patients, no signs of obstruction of the biliary tract. In laboratory studies, a tendency to anemia was found in the blood (a decrease in the level of red blood cells and hemoglobin, hematocrit (Ht) was reduced, the number of reticulocytes in the blood was normal or slightly elevated, the serum iron level was normal or moderately lower, the OJSS was normal or decreased, moderate leukocytosis, moderate increase in ESR, hyperbilirubinemia with a predominant increase in the conjugated fraction, a moderate increase in the activity of alanine aminotransferase, in some patients - an increase in the activity of alkaline phosphatase, gammaglutamyltranspeptidase, hypercholesterolemia.

Prior to the start of treatment in both groups, we observed similar changes in clinical immunity parameters characterized by T-lymphopenia, a decrease in the number of T-helper / inducers circulating in the blood (CD4 +) and an imbalance in the subpopulation composition of T cells with a decrease in the immunoregulatory

CD4 / CD8 index relative to the norm that speaks about the formation in patients with CKTP and AChs on the background of the transferred pulmonary tuberculosis more often with respect to the suppressor variant of immunodeficiency (with the predominant decrease in the number of cells with helper activity Yu). In connection with general T-lymphopenia, the absolute number of lymphocytes with the CD8 + phenotype also moderately decreased, however, to a slightly lesser extent than the number of lymphocytes with the CD4 + phenotype (table).

Thus, the immunoregulatory index of CD4 / CD8 in all of the examined patients with CTLD and AChs was significantly lower than the norm ( $P < 0.001$ ) in the presence of pulmonary tuberculosis. The number of B cells (CD22 +) in most cases did not change significantly in relative value, whereas the absolute number of B-lymphocytes in patients was significantly reduced (Table). At the same time, the functional activity of T-lymphocytes in the examined patients for this combined diagnosis was significantly reduced: in the main group, an average of 1.82 times the norm ( $P \square 0.01$ ) and in the comparison group 1.74 times ( $P \square 0.01$ ).

Thus, before the beginning of the treatment, the examined patients of both groups had quite significant disorders from the cell link of immunity. They consisted in the presence of T-lymphopenia, an imbalance in the subpopulation composition of T lymphocytes with a predominant decrease in the number of T helper / inducers (CD4 +) circulating in the peripheral blood and a decrease in the immunoregulatory index of CD4 / CD8. The number of lymphocytes with the CD8 + phenotype (T suppressor / killer) and CD22 + (B-lymphocytes) did not decrease in relative amounts, however, due to general lymphopenia, the absolute number of CD8 + and CD22 + lymphocytes decreased moderately. At the same time, there was a significant decrease in the functional activity of T-lymphocytes according to RTBL data.

In a second study of

the cellular response of the immune response after completion of the treatment, we found that in the main group of patients (who received a combination of sirep and sodium nucleate), the amount of CD3 + cells (total population of T-lymphocytes) and T-helper / inducers CD4 +) almost completely normalized, in connection with which the immunoregulatory index CD4 / CD8 rose to normal. It is significant that along with the normalization of the quantitative indices of the T-cell link of immunity, the restoration of the functional activity of T-lymphocytes was also noted in the examined patients, which is confirmed by the dynamics of RBTL with PHA. Indeed, in the patients of the main group (who received the combination of sirepah and sodium nucleate), the indicator of RBTL with PHA increased from  $38.6 \pm 3.0\%$  to  $68.2 \pm 2.4\%$ , that is, 1.76 times the baseline and reaches lower limit of the norm (table). Thus, under the influence of a combination of sirepar and sodium nucleate preparations in patients with CTLD and AChs on the background

**Dynamics of cellular immunity indices in patients with CKTP and AChs on the background of the transferred pulmonary tuberculosis during treatment (M $\pm$ m)**

Immunological parameter	Norm	Group of patients	
		the main (n=34)	comparison (n=32)
CD3+. %	69.8 $\pm$ 2.1	$\frac{51.3 \pm 2.0^{**}}{67.9 \pm 0.2}$	$\frac{50.9 \pm 1.8^{**}}{56.3 \pm 0.9^*}$
г/л	1.32 $\pm$ 0.04	$\frac{0.87 \pm 0.01^{***}}{1.25 \pm 0.04}$	$\frac{0.85 \pm 0.03^{***}}{0.95 \pm 0.04^{**}}$
CD4+. %	45.6 $\pm$ 1.5	$\frac{30.3 \pm 1.9^{**}}{43.6 \pm 2.0}$	$\frac{30.9 \pm 1.8^{**}}{35.8 \pm 2.1^*}$
г/л	0.87 $\pm$ 0.03	$\frac{0.46 \pm 0.01^{***}}{0.80 \pm 1.3}$	$\frac{0.5 \pm 0.02^{***}}{0.60 \pm 1.4^{**}}$
CD8+. %	22.3 $\pm$ 0.9	$\frac{18.5 \pm 0.1}{21.5 \pm 2.5}$	$\frac{19.0 \pm 0.2}{21.3 \pm 2.1}$
г/л	0.42 $\pm$ 0.02	$\frac{0.29 \pm 1.1^*}{0.38 \pm 0.01}$	$\frac{0.3 \pm 1.0^*}{0.33 \pm 0.02^*}$
CD4/CD8	2.04 $\pm$ 0.03	$\frac{1.58 \pm 0.02^{***}}{2.1 \pm 0.03}$	$\frac{1.6 \pm 0.02^{***}}{1.81 \pm 0.03^{**}}$
CD22+. %	21.6 $\pm$ 1.1	$\frac{19.7 \pm 0.2}{21.2 \pm 1.3}$	$\frac{20.1 \pm 0.3}{20.9 \pm 1.4}$
г/л	0.41 $\pm$ 0.02	$\frac{0.31 \pm 0.01^*}{0.37 \pm 0.02}$	$\frac{0.3 \pm 0.03^*}{0.35 \pm 0.02}$
RTBL with PHA. %	69.5 $\pm$ 2.3	$\frac{38.6 \pm 3.0^{**}}{68.2 \pm 2.4}$	$\frac{39.1 \pm 2.7^{**}}{50.9 \pm 2.5^*}$

Note: in the numerator - indicators before the start of treatment, in the denominator - after its completion; the probability of a difference in the indicators relative to the norm: \* - for  $P < 0.05$ , \*\* -  $P < 0.01$ , \*\*\* -  $P < 0.001$ .



of transferred infiltrative pulmonary tuberculosis, normalization of both quantitative and functional indices of the T-cell link of the immune response is noted. Concerning the number of CD8 + and CD22 + lymphocytes in patients of the main group, these indicators also normalized (table).

In the comparison group, we also noted a positive dynamics of the studied indices of the cellular immunity, but it is much less pronounced. Therefore, after the completion of treatment in the comparison group patients, there are shifts between the majority of the immunological parameters studied, both in relation to the main group and the corresponding norm indicators (table). Thus, a significant difference in the number of T-cells (CD3 +) was established between the groups of patients both in relative terms (an average of  $11.6 \pm 0.7\%$ ,  $P < 0.05$ ), and in calculating the absolute number (in 1.3 times,  $P < 0.05$ ). The relative number of CD4 + lymphocytes in the comparison group after completion of treatment was  $7.2 \pm 0.5\%$  lower than in the main group ( $P < 0.05$ ), and the absolute number of CD4 + cells was 1.3 times ( $P < 0.05$ ). The immunoregulatory index of CD4 / CD8 after the completion of the course of treatment in the main group was 1.16 times higher than in the comparison group ( $P < 0.05$ ), the indicator of RBTL with PHA was 1.33 times higher ( $P < 0.05$ ).

Thus, the obtained data indicate that the use of a combination of sireppara and sodium nucleate helps to restore the indices of immunological homeostasis in patients with CKTP and AChs on the background of the transferred pulmonary tuberculosis, namely, it ensures the elimination of T-lymphopenia, the normalization of the relation between the helper and suppressor subpopulations of T cells, an increase in the indicator of RBLT from the PHA.

It is significant that in the clinical plan, the use of sirepar and sodium nucleate in the treatment of drugs, accompanied by an improvement in the well-being and general condition of the patients, primarily a reduction in general weakness, malaise, increased capacity for work and appetite, and improved mood, disappeared in the right hypochondrium, the sub-skin and sclera. In the comparison group, we also noted a positive dynamics of clinical indicators, but less pronounced. When analyzing biochemical parameters, it was found that the activity of serum aminotransferases practically normalized in patients of the main group (96% of patients).

Thus, the obtained data testify that the use of a combination of sirepar and sodium nucleate preparations in the complex of treatment of patients with CTLD and AChs with pathology of lung tuberculosis is pathogenetically sound and clinically effective, since this combination of drugs contributes to both elimination of clinical and biochemical manifestations of the disease and normalization of indices of immunological homeostasis, namely the state of the cellular link of immunity. There were no any side effects from the use of the proposed combination of drugs, including allergic reactions.

**Conclusions.** 1. The clinical picture of CTLD and AChP in the presence of infiltrative pulmonary tuberculosis is characterized by the presence of varying degrees of asthenic, asthenic-neurotic, mild cytolytic syndromes, anemia, hepatomegaly, in some patients - cholestatic, as well as characteristic changes in the chest radiograph

2. Immunological examination revealed violations of the cellular immunity, characterized by T-lymphopenia, an imbalance in the subpopulation composition of T-lymphocytes, mainly by reducing the number of circulating lymphocytes circulating in the peripheral blood, having a CD4 + (T helper / inducer) phenotype and an immunoregulatory CD4 index / CD8, a significant decrease in the functional activity of T cells according to the data of RBTL with PHA. In general, the obtained data indicate the formation of a secondary immunodeficiency state, mainly on a relatively suppressor version.

3. The use in the treatment of patients with CTLD and AChs on the background of the transferred pulmonary tuberculosis, a combination of preparations of sirepar and sodium nucleate contributes to the elimination of the clinical phenomena of the combined pathology, and along with the improvement or complete normalization of clinical parameters in the patients examined, there was an improvement in biochemical parameters characterizing the functional state liver.

4. In patients who received a combination of sirepar and sodium nucleate, the normalization of the cellular immunity parameters was noted, which gives grounds for recommendations on the use of the proposed combination of drugs in complex treatment.

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## CYTOLOGICAL ANALYSIS OF CERVIX INFLAMMATORY DISEASES IN DIFFERENT AGE GROUPS ON THE EXAMPLE OF THE SAKHA (YAKUTIA) REPUBLIC

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### ABSTRACT

Cytological analysis of cervix inflammatory diseases was conducted on women aged 18 to 88. The results of the analysis showed a high incidence of disease in the age groups 18-29. In the middle age group (30-44 and 45-59 years), balancing of genital infections is noted and the first effects of infection with viral infections appear (dysplasias of varying severity and background changes in the epithelium). In women in the older age group, mainly inflammatory processes (atrophic colpitis) were observed, which is associated with the intense influence of sex hormones. Generally, long-term preservation of viral HPV is associated with high-oncogenic risk types of HPV infection (mainly HPV 16). Remote causes of viral infection were found rarely (2.9%) on menopause, but it has the important prognostic value, which can predict the risk of cervical pathology development. Inflammation processes (senile vaginitis) are found in the old age group of women (20.9%), which is due to the intensive influence of sex hormones (estrogens). At this period the lack of estrogen harms the main protective properties of the stratified squamous epithelium. As a result, the number of lactobacilli is decreased or completely disappeared by the cause of conditionally pathogenic and pathogenic flora overgrowth.

Thus, infectious-inflammatory diseases of the female genital organs caused by various pathogens, sexually transmitted diseases, or nonspecific microflora, represent a serious medical and social problem.

**Keywords:** oncocytopology, diagnostics, inflammation.

**Relevance.** Pelvic inflammatory diseases (PID) establish itself as a leading position in the structure of gynecological disorders, also become the most common cause of women's reproductive system disability. Thereby, it creates a major health, social and economic problems worldwide [2, 7, 10, 11, 13, 15].

The starting moment for the progression of acute inflammatory diseases is the invasion of microorganisms. Cervix is an important protective barrier on the way for plaque formation in the internal genital organs. Almost all microorganisms those present in the vagina, except for lactobacillus and bifidobacteria, can be involved in the development of the inflammatory process [4]. However, in most cases, PID is caused by sexually

transmitted infections [8, 12]. The immune system takes an important part in the pathogenesis of female genital organs inflammation. Inflammation and immune process are inextricably linked, and currently, inflammatory and immune responses are considered as a complete whole [9]. Notice that at the beginning of the pathological process only one infectious agent activates the inflammatory response, changes local immune system functioning. Thereby it prepares the breeding ground for further contamination with opportunistic pathogens [8, 14].

There are different factors in cervix inflammatory process: bacterial imbalance; thinning of stratified squamous epithelium in postmenopausal years along with the inflammatory process

(senile vaginitis); various physical and chemical effects; earlier diseases that harm the immunity system; infections [1].

Modern PID is a problem of sexually active women. Recently most researchers find out that social factors take the main part in the genesis of the PID progression, such as early sexual debut, high sex frequency, high number of sexual partners, sexual activity during menstruation, using of drugs [6, 16]. Many scientists consider that genital inflammatory process is the onset of majority gynecological diseases. According to V. N. Serov et al, chronic inflammatory process in the genital organs responsible for the formation of such pathology as endometriosis, uterine fibroid, hyperplastic processes, infertility of various origins, neoplastic diseases

of the cervix, as well as functional disorders that violate the normal course of pregnancy [5].

Chlamydia and trichomonas viruses have the most severe course and complications for women's health.

The importance of inflammatory infection of the female genital system primarily determined by the fact that this disease affects organs and tissues of reproductive function. The Imbalance of bacteria in the vagina can be asymptomatic in almost half of affected women. Usually, it has no any signs of disease, and remains without medical treatment [9].

The aim of the study: to determine the incidence of cervix inflammatory diseases among women of different age groups.

**Materials and methods.** Cytological material of cervix has been analyzed in M.K. Ammosov NEFU Medical clinic laboratory of pathomorphology, histology, and cytology. Material was taken from 7600 women aged 18 to 88, who appealed to various medical centers of the Sakha (Yakutia) Republic for prophylactic and diagnostic purposes during 2017.

Material for the cytological study was smears taken from the cervical mucosa and cervical canal. Eliseev (2007) age classification was applied to identify trends of the epidemic process in different age groups. According to it, persons from 18-29 are young age, from 30-44 are mature age, from 45-59 are middle age, from 60-74 are old age [3].

The diagnosis was conducted by Romanovsky-Gimza staining method. Cytological diagnosis was determined according to the clinical and morphological classification of Bohman (1976).

**Results and discussion.** The age composition of the studied was as follows: from 18 - 29 years - 2645 women (34,8%), 30-44 years – 2315 women (30,4%), 45-59 years – 1840 women (24,2%) and 60 years and over - 800 women (10.5 %).

Results of the cytological examination (table 1) diagnosed cervix inflammatory disease in 4629 cases; it is about 61% of the total investigated women. In the different age groups we registered the highest rate in the 18-29 years – 1696 cases (36.6%), and 30-44 years – 1407 cases (30,4%). In women aged 45-59 years 1065 PID cases were noted (23%).

In most cases 1815 (39.2%) studied women had flora dysbiosis (bacterial vaginosis (BV) and Lactobacillus).

**Note: in the numerator - indicators before the start of treatment, in the denominator - after its completion; the probability of a difference in the indicators relative to the norm: \* - for  $P < 0,05$ , \*\* -  $P < 0,01$ , \*\*\* -  $P < 0,001$ .**

	Age				
	18-29	30-44	45-59	60 years and older	Total
Inflammatory process	540 (29.8%)	348 (19.2%)	542 (29.9%)	379 (20.9%)	1809 (39%)
Flora dysbiosis	740 (40.7%)	693 (38.2%)	337 (18.5%)	45 (2.5%)	1815 (39.2%)
Candidal colpitis	57 (49.5%)	38 (33%)	17 (14.8%)	3 (2.6%)	115 (2.5%)
Trichomonas colpitis	29 (49.1%)	16 (27.1%)	13 (22%)	1 (1.7%)	59 (1.3%)
Follicular cervicitis	47 (49.5%)	25 (26.3%)	13 (13.7%)	10 (10.5%)	95 (2%)
Remote causes of chlamydia	14 (29.7%)	18 (38.3%)	12 (25.5%)	3 (6.4%)	47 (1%)
Remote causes of viral infection	269 (39%)	269 (39%)	131 (19%)	20 (2.9%)	689 (14.9%)
Total	1696 (36.6%)	1407 (30.4%)	1065 (23%)	461 (9.9%)	4629 (61%)

Cytogram of the inflammatory process marked by the presence of so-called mixed bacterial flora, leukocytosis and reactive changes of the epithelium.

Maximum incidence observed in the age group of 18-29 years - 740 cases (40.7 %) and 30-44 years 693 cases (38.2 %). Next by incidence of occurrence was inflammatory processes in 1809 cases (39%). The highest incidence was recorded in the age groups of 45-59 years – 542 cases (29.9%) and 18-29 – 540 cases (29.8%).

Currently, the greatest interest among sexually transmitted infections represents the human papillomavirus (HPV). The main cytological feature is the presence of the so-called koilocytes, cells of layered epithelium with an extensive perinuclear region of enlightenment of cytoplasm, and with a characteristic arrangement of nuclei («kissing») in smears (fig.2).

The study of remote causes of viral infection were determined in 689 cases, which composed 14.9% of the total number of inflammatory diseases. In general, the maximum incidence of this pathology registered on women of active reproductive age from 18 to 44 years, 269 cases (39%) (fig.3). These women are recommended to test HPV. The highest response has a method of polymerase chain reaction (PCR), unfortunately, there is no data on post-process treatment, including PCR. The complete virus-eliminating occurs in a carrier with a good immunological status. This explains the disappearance of the cytopathic effect of viral infection in the additional smear of HPV carrier.

Candidal colpitis was registered among 115 (2.5 %) women: budding yeast cells, spores and pseudomycelium in smears (fig.4).

Much less follicular cervicitis (postmenopausal) and chronic inflammation (of childbearing age) is diagnosed and detected in 2% of cases from the total number of inflammatory diseases. The maximum incidence is

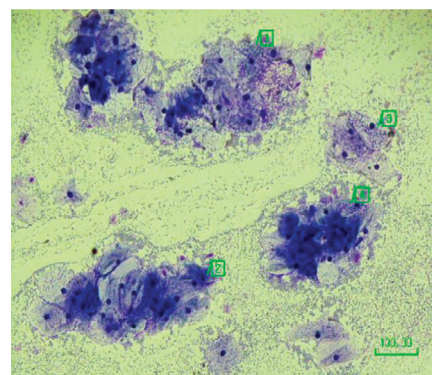
noted in age groups of 18-29 years, 47 cases (49.5 %) and 30-44 years, 25 cases (26.3%). Cytological results of this pathology are characterized by the presence of lymphoid elements (fig.5).

In most cases, trichomonas vaginitis (1.3% of cases from total number of PID) were found in age group of 18 -29 years, 49.1% (fig.6).

Urogenital chlamydiosis is one of the most common sexually transmitted infections. According to our data, 47 cases (1%) were diagnosed with remote causes of chlamydial infection (fig.7). The highest incidence was registered in the age group of 30-44 years (38.3 %). The data of cytological examination in the detection of chlamydial infection are indicative and should be supplemented by other research methods (immunofluorescence analysis, polymerase chain reaction, etc.).

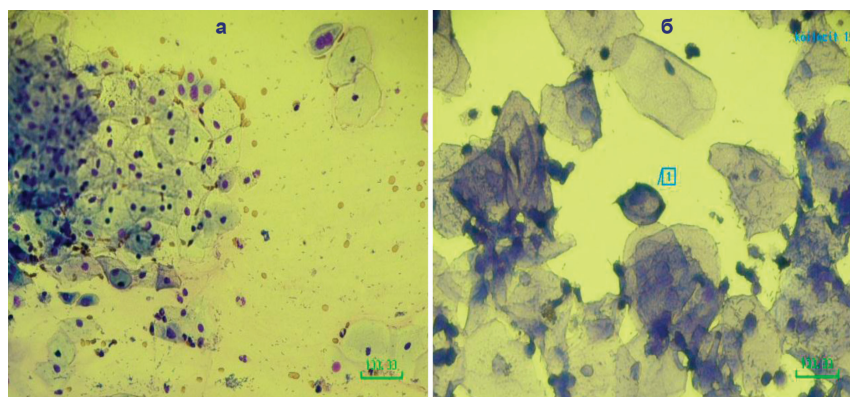
**Conclusion:** Hereby, the results of cytological examination (fig.8) revealed that inflammatory diseases of sexually transmitted infections dominate among women aged 18-29 years (49.5%).

The main reason is the increased sexual behavior of young people, which registered at this age period. Frequent sexual partners changes are causes dysbiosis of the vaginal flora. Usually, chronic inflammation occurs on young



**Fig.1.** The abundance of small bacteria, «clue cell» in their smear ectocervix with bacterial vaginosis, x200





**Fig.2.** Binuclear or «kissing» nuclei in cervix smear for papillomavirus infection (conventional smear) and koilocyte for liquid-based cytology (staining method by Romanovsky-Gimza), x400

women, who take oral contraceptives and using the intrauterine device. In the middle age group (30-44 and 45-59), genital infections and dysbiosis are balanced, which associated with a stabilization of family relations.

The maximum frequency of remote causes of viral infection depends on age that shows the peak detection in the age groups of 18-29 years and 30-44 years. HPV infection disappears by itself within 12 months after diagnosis date in about 70% of young women cases. Generally, long-term preservation of viral HPV is associated with high-oncogenic risk types of HPV infection (mainly HPV 16) [2]. Remote causes of viral infection were found rarely (2.9%) on menopause, but it has the important prognostic value, which can predict the risk of cervical pathology development.

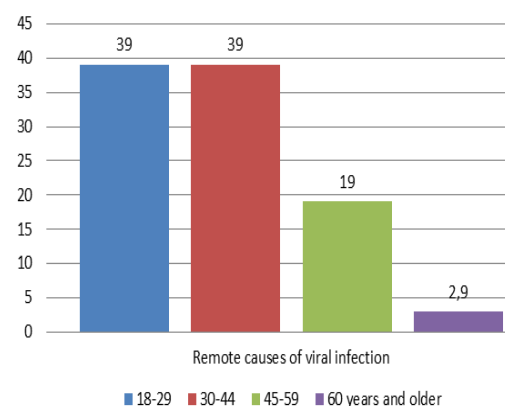
Inflammation processes (senile vaginitis) are found in the old age group of women (20,9%), which is due to the intensive influence of sex hormones (estrogens). At this period the lack of estrogen harms the main protective properties of the stratified squamous epithelium. As a result, the number of lactobacilli is decreased or completely disappeared by the cause of conditionally pathogenic and pathogenic flora overgrowth.

Thus, infectious-inflammatory diseases of the female genital organs caused by various pathogens, sexually transmitted diseases, or nonspecific microflora, represent a serious medical and social problem.

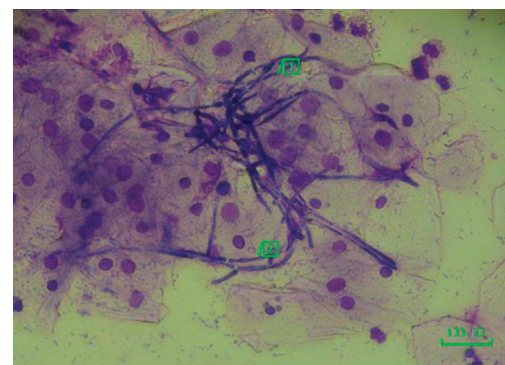
*This work is based on R&D "Epidemiology aspects of cancer on the Far North living environment, development of methods for the prevention, diagnosis, treatment using the high-informative basic research methods (M06;01;01)" (№ 0556-2014-0006).*

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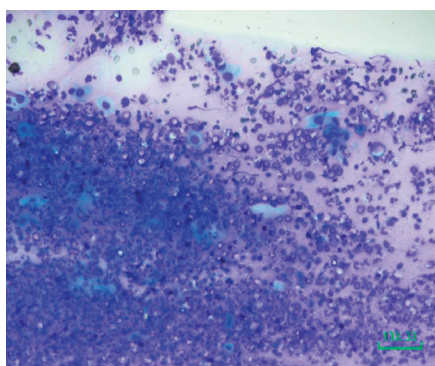
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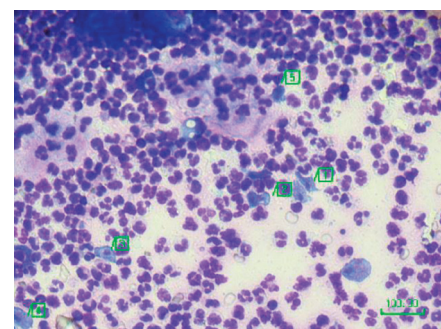
**Fig.3.** The frequency occurrence of remote causes of viral infection in different age groups



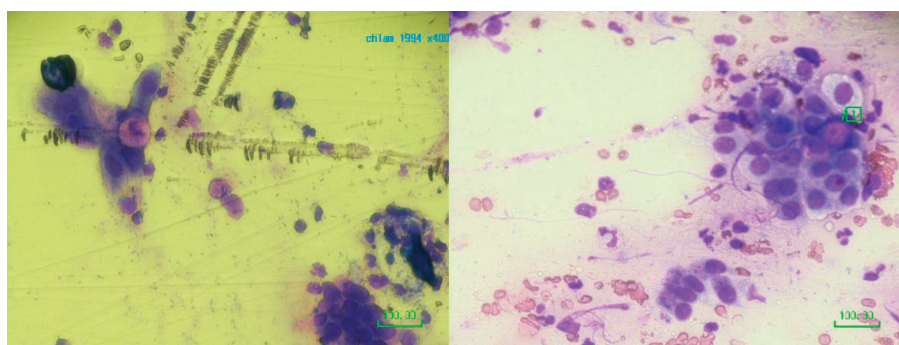
**Fig.4.** Thrush. Pseudomycelium and fungal spores in the smear from the cervix, x400



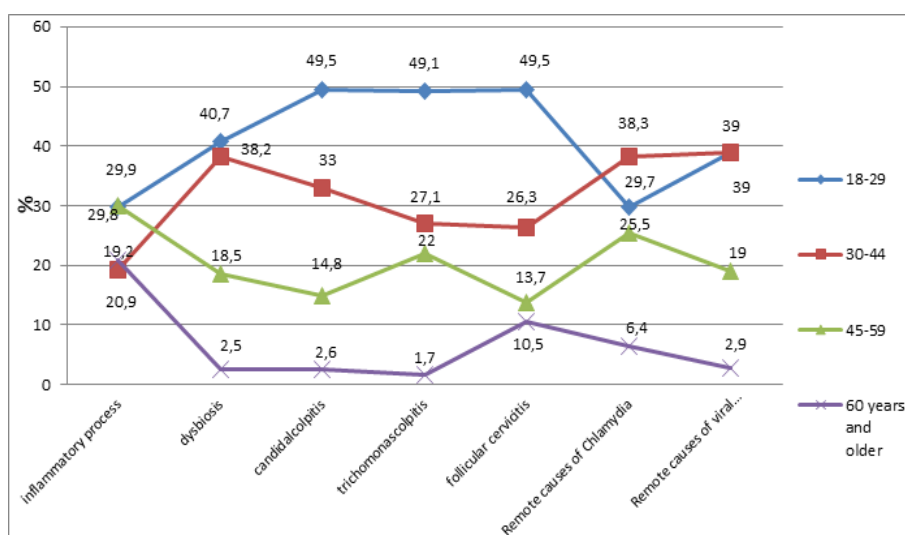
**Fig.5.** Follicular cervicitis. x200



**Fig.6.** Trichomonas and leucocytes in a smear from the ectocervix with trichomonas colpitis. X400



**Fig.7.** Layers of metaprotegerol epithelium cells with vacuoles of various size, which contain fills associated with different stages of the chlamydial infection development. x400



**Fig.8.** The rate of incidence of cervix inflammatory diseases among women of different age groups

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## EVALUATION OF GLUTATHIONE SYSTEM INDICATORS IN THE BODY OF PATIENTS WITH LUNG CANCER

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#### ABSTRACT

Glutathione is very important in cells protecting, however, its high concentration in tumor cells can increase their survival by raising resistance to chemotherapeutic drugs and free radical oxidation. The effectiveness of chemotherapy treatment often depends on the individual genetic characteristics of the patient, his sensitivity to pharmaceutical drugs. According to scarce existing research it is indicated that tolerability of chemotherapy among Asians is lower compared to Caucasians. In this regard, we decided to evaluate the influence of ethnicity on the indicators of the glutathione system in patients with lung cancer and persons not suffering from oncopathology.



We examined 50 people with lung cancer, admitted to the Yakut Republican Oncology Center. The control group was selected based on age, gender and ethnicity and included 50 people. The main criterion for selection in the control group was the absence of cancer.

The concentration of reduced glutathione, TBA-active products, activity of glutathione reductase, glutathione-S-transferase, glutathione peroxidase were determined by the spectrophotometric method.

The results of our study showed that the concentration of reduced glutathione (Yakuts by 70.7, Russians by 52.4%), the activity of glutathione peroxidase (Yakuts by 34.4, Russians by 18.6%) in the body of patients had been decreasing. The activity of glutathione reductase in the body of patients with lung cancer decreased in Yakuts by 10.5%, while in Russians it increased by 13.0%. The results of our research testify to the depletion of the glutathione system in the group of cancer patients of the Yakut ethnicity, which is probably the reason for the severe tolerance of chemotherapy.

**Keywords:** glutathione peroxidase, glutathione reductase, glutathione-S-transferase, reduced glutathione, TBA-active products, glutathione system.

**Introduction.** Glutathione is an intracellular tripeptide consisting of the amino acids: L-glutamate, L-cysteine and L-glycine, it is present in the cells of all eukaryotes, including tumor cells. The concentration of glutathione in the cells is very high, reaching from 1 to 10 mM [15]. The main reservoirs of this tripeptide in the cell are: cytosol (90%), mitochondria (10%) and a small percentage falls to the share of the endoplasmic reticulum [13]. The glutathione metabolism proceeds fairly quickly, for example, in the liver of rats, the period of its half-life is only 2-3 hours [4].

Glutathione readily reacts with electrophilic compounds (carcinogens, drugs), reducing their toxicity [14]; in the nucleus, it promotes the repair of damaged DNA [3]; neutralizes free radicals and peroxides [11]; provides active transport of amino acids [6]; participates in the modulation of the immune response [8], regulates the redox state of the thiol proteins NFkB, caspase, which are involved in apoptosis [12]. It should be noted that glutathione is very important in cells protecting, however, a high concentration of glutathione in tumor cells can increase their survival by increasing their resistance to chemotherapeutic drugs and free radical oxidation [5].

The effectiveness of chemotherapy treatment often depends on the individual genetic characteristics of the patient, his sensitivity to pharmaceutical drugs [9, 16]. According to scarce existing research it is indicated that tolerability of chemotherapy among Asians is lower compared to Caucasians [7]. In this regard, we decided to evaluate the influence of ethnicity on the indicators of the glutathione system in patients with lung cancer and persons not suffering from oncopathology.

The **objective** of this study is to assess the level of glutathione levels in the body of patients with lung cancer.

#### Research materials and methods.

50 people with lung cancer, admitted to the Yakut Republican Oncology Center were under study. The diagnosis of lung cancer was confirmed histologically. The patients were divided into two groups according to ethnicity: the first group is the Yakuts, the second group is the Russians. The control group was selected

based on age, gender and ethnicity and included 50 people. The main criterion for selection in the control group was the absence of cancer. The study material was venous blood, which was taken on an empty stomach from the ulnar vein.

The concentration of indicators of the glutathione system was determined in erythrocytes, and the level of TBA-AP in blood serum using SF-2000 spectrophotometer. The content of reduced glutathione was determined by the reaction with 5,5-dithiobis (2-nitrobenzoic acid) at 412 nm and was expressed in  $\mu\text{M/gHb}$  [2]. Glutathione reductase activity was determined by the oxidation rate of NADPH + in the presence of oxidized glutathione at 340 nm and expressed in  $\mu\text{MGSSG/min} \cdot \text{gHb}$ . Glutathione-S-transferase activity was determined at 340 nm by the rate of formation of conjugates with 1-chloro-2,4-dinitrobenzene in the presence of reduced glutathione and expressed in  $\mu\text{M GSH / min} \cdot \text{g Hb}$  [10]. Glutathione peroxidase activity was determined at 412 nm in the tertiary butyl hydroperoxide cleavage reaction using reduced glutathione as a substrate. The enzyme activity was expressed in  $\mu\text{M GSH / min} \cdot \text{gHb}$  [1]. The level of TBA-AP was determined by the reaction of the end products of free radical oxidation of lipids with thiobarbituric acid to form a colored trime-thine complex, which was measured at a wavelength of 532 nm and expressed in  $\mu\text{M / L}$  [17].

Statistical processing of the data was performed using the SPSS for Windows 10.0 application statistical software package. Standard methods of variation statistics were used: calculation of averages, standard errors, 95% confidence interval. The significance of differences between averages was evaluated using Student's t test for independent samples. The data in the tables are presented as  $M \pm m$ , where M is the average, m is the average error. The probability of the validity of the null hypothesis was taken at  $p < 0.05$ .

**Results and discussion.** According to our data, the content of reduced glutathione in the group of relatively healthy people not suffering from oncopathology was  $2.32 \pm 0.09 \mu\text{M / gHb}$ . The concentration of reduced glutathione changed depending on ethnicity: in the first group

it was  $2.50 \pm 0.05 \mu\text{M / gHb}$ , in the second -  $2.04 \pm 0.06 \mu\text{M / gHb}$ , that is, in the Yakuts it was higher by 18.4%, compared to the Russians.

Glutathione reductase activity was  $6.8 \pm 0.30 \mu\text{M GSSG / min} \cdot \text{g Hb}$ . The level of the average activity of glutathione reductase in the first group ( $7.5 \pm 0.10 \mu\text{MGSSG / min} \cdot \text{gHb}$ ) was 20% higher ( $p < 0.05$ ) than in the second ( $6.01 \pm 0.30 \mu\text{MGSSG / min} \cdot \text{hb}$ ).

Glutathione-S-transferase activity was  $2.44 \pm 0.07 \mu\text{MGSH / min} \cdot \text{gHb}$ . We observed a decrease in the activity of glutathione-S-transferase in the first group ( $2.20 \pm 0.06 \mu\text{M GSH / min} \cdot \text{gHb}$ ) by 9% compared with the second group ( $2.42 \pm 0.03 \mu\text{M GSH / min} \cdot \text{gHb}$ ).

The level of glutathione peroxidase was  $6.10 \pm 0.005 \mu\text{M GGSHP / min} \cdot \text{gHb}$ . Depending on the ethnicity, differences in enzyme activity were noted: in the first group ( $6.50 \pm 0.009 \mu\text{M GGSHP / min} \cdot \text{gHb}$ ), it was significantly higher (by 35.4%) than in the second ( $4.20 \pm 0.002 \mu\text{M GH / min} \cdot \text{gHb}$ ).

The concentration of the lipid peroxidation index - TBK-AP was equal to  $1.61 \pm 0.10 \mu\text{M / l}$  and depended on ethnicity. So, in the first group this indicator corresponded to  $1.71 \pm 0.16 \mu\text{M / l}$ , in the second -  $1.38 \pm 0.28 \mu\text{M/l}$ , i.e. in the first group, the level of TBA-AP was higher by 19.3% ( $p < 0.05$ ).

Depending on the ethnicity of relatively healthy individuals, the indicators of the glutathione system change. In the Yakut group higher concentrations of reduced glutathione (18%), glutathione reductase activity (20%) and glutathione peroxidase (35.4%) are noted. We also noted the intensification of free radical oxidation of lipids in the body of Yakuts, as evidenced by an increase in the concentration of TBA-AP by 19.3%.

In the body of patients with cancer, the concentration of reduced glutathione was significantly lower (by 28.8%) compared with those not suffering from oncopathology and was equal to  $1.65 \pm 0.01 \mu\text{M / gHb}$ . This can probably be caused by a high rate of consumption and a low rate of its recovery. Maintaining a sufficiently high level of reduced glutathione by restoring its disulfide form is provided by glutathione reductase. Glutathione reductase activity in the group of patients

was less by 36.7% than in the control, and was  $4.30 \pm 0.05 \mu\text{M GSSG} / \text{min} \cdot \text{g Hb}$ . Consequently, the regeneration of glutathione in the blood erythrocytes of patients with lung cancer at the proper level does not occur. We consider the most likely cause of this phenomenon an insufficient regeneration of  $\text{NADPH} + \text{H}^+$  in the pentose phosphate pathway. The activity of glutathione-S-transferase did not actually differ from the control, it was equal to  $2.42 \pm 0.01 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ . Glutathione peroxidase activity decreased by 68.8% ( $1.9 \pm 0.001 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ ) than in the control group. In patients with lung cancer, a significant increase in free radical oxidation of lipids was noted. The average content of TBA-AP in the blood of patients with lung cancer was 32.6% higher than the control value and was  $2.39 \pm 0.32 \mu\text{M/L}$ .

In the group of patients, the concentration of the reduced form of glutathione, as well as the activity of glutathione reductase, did not have significant differences depending on ethnicity. In the first group of patients, the content of reduced glutathione was 34.4% less ( $P < 0.05$ ) compared with the control group ( $1.64 \pm 0.01 \mu\text{M} / \text{gHb}$ ), in the second group of patients it was 18.6% lower ( $P < 0.05$ ) ( $1.66 \pm 0.009 \mu\text{M} / \text{gHb}$ ). Glutathione reductase activity in the first group of patients was 10.5% lower ( $6.71 \pm 0.09 \mu\text{M GSSG} / \text{min} \cdot \text{gHb}$ ), and in the second group of patients it was 13.0% higher than control ( $6.9 \pm 0.15 \mu\text{M GSSG} / \text{min} \cdot \text{hb}$ ).

Significant differences in the activity of the enzyme performing the detoxification function in patients with lung cancer, depending on ethnicity, were not found. Glutathione-S-transferase activity in the first group of patients was 7.1% ( $2.37 \pm 0.15 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ ), in the second group 3.0% ( $2.49 \pm 0.25 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ ) above the control value.

An assessment of the enzymatic status of antioxidant protection in the blood of patients with lung cancer showed that glutathione peroxidase activity in both groups of patients was significantly reduced. In the first group, the glutathione peroxidase activity was 70.7% less than the control ( $1.90 \pm 0.005 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ ); and in the second group - by 52.4% ( $2.00 \pm 0.012 \mu\text{M GSH} / \text{min} \cdot \text{gHb}$ ).

At the same time, the intensity of free radical oxidation in the body of cancer patients increased, as evidenced by the increase in the content of TBA-AP in patients of the first group to  $2.35 \pm 0.12 \mu\text{M} / \text{L}$ , which was 27.2% higher than the control ( $P < 0.01$ ), the second group was equal to  $2.45 \pm 0.25 \mu\text{M} / \text{L}$ , which exceeds the control indicators by 43.6% ( $P < 0.05$ ).

**Conclusions.** Thus, the results of

our research have shown that in patients with lung cancer, indicators of the glutathione system vary depending on ethnicity. Among patients the concentration of reduced glutathione in the Yakuts decreased by 34.4%, Russians - by 18.6%, glutathione peroxidase activity - by 70.7 and 52.4%, respectively. The activity of glutathione reductase in the body of patients with lung cancer decreased in the Yakuts by 10.5%, while in the Russians it increased by 13.0%. The results of our research testify to the depletion of the glutathione system in the group of cancer patients of the Yakut ethnicity, which is probably the reason for the severe tolerance of chemotherapy.

*This study was conducted in the framework of the research work "Epidemiological aspects of malignant tumors in the conditions of the Far North, the development of modern methods for early diagnosis, prevention using highly informative fundamental research methods" in the department of studying the adaptation mechanisms of the Yakut Science Center of Complex Medical Problems.*

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## ASSESSMENT OF CHANGE OF ERYTHROCYTES BY METHOD OF RASTER ELECTRONIC MICROSCOPY AT THE PERSONS WHO DIED OF FATAL HYPOTHERMIA

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#### ABSTRACT

Red blood cells (RBC) morphology of deceased from various causes (injury, hypothermia) was examined in this study by using scanning electron microscopy. The obtained data shows that the appearance of certain forms of cadaveric erythrocytes depends on the causes of death. Therefore, when death is caused by stabbing and gunshots RBC take acanthocyte forms and in cases of fatal hypothermia RBC take echinocyte forms. The results of an experiment carried out in vitro, at small negative temperatures, show the appearance of acanthocytes in observed blood samples. Based on the obtained data and on the ability of echinocyte to return to normal form, it can be concluded that the probability of restoring the vital activity of the frozen organisms are possible.

**Keywords:** red blood cells, erythrocytes, hypothermia, scanning electron microscopy.

**Introduction.** Frostbite and hypothermia are the most severe types of cold trauma, often leading to a high level of disability and death of the affected [1]. Till present time, the questions of death from freezing in conditions of extremely low temperatures (below -40°C) have not been fully examined in the world. In real conditions, people who died from hypothermia (by external signs) without carrying out resuscitation measures are delivered to the morgue. The key-point

is that during the first 2 days when the victims are in a state of cold anabiosis (a very rare pulse, low blood pressure) it is may be possible to restore the vital activity of the organism (there are cases of preservation of the vital functions of the heart and other organs in frozen animals). The results of our work suggest a theoretical probability of the restoration of frozen tissues, organs, and also the revitalization of the frozen organisms.

At present time, in the literature

available to the public, there are no data on the SEM study of the RBCs of people who died from the cold temperatures.

Revealing the features of the morphology of the blood cells of the deceased from hypothermia may possibly supplement the idea of the cellular-molecular mechanisms of the process of general cooling of the organism and confirm the possibility of restoring the vital activity of the organism.

The purpose of this article is to examine



the morphological changes in RBCs from cadaveric material (cause of death: hypothermia) using a scanning electron microscopy.

#### Materials and methods of research.

The study was carried out using a high-resolution scanning electron microscope (SEM) JSM-7800F («Japanese Electron Optics Laboratory» - «JEOL», Japan) in UNTL «Graphene nanotechnology» M.K. Ammosov NEFU. The subjects of the study were blood smears from cadaveric material of the deceased from various causes of death, including hypothermia prepared by the Bureau of Forensic Medical Examination of the Ministry of Health of the Republic of Sakha (Yakutia).

The device has a Schottky thermofield emission cathode and a superhybrid objective lens that significantly reduces chromatic and spherical aberration and significantly increases the resolution, especially at low accelerating voltages. The SEM used in the experiment (enlargement range of 25 - 1 000 000) allows us to examine the object at an accelerating voltage of 0.1-30 kV. The device is equipped with 4 types of detectors: the upper electron detector, the upper secondary electron detector, the backward reflected electron detector and the lower secondary electron detector. In this study a lower secondary electron detector was used. This mode allows reducing the effect of electrostatic charge on the surface of the sample, which significantly improves the image quality of the erythrocyte surface.

Used in the study of blood smears, the SEM JSM-7800F is equipped with the «Gentle Beam» system, which allows to reduce the speed of electrons falling on the sample and accelerate the electrons emitted by them, which significantly improves image quality at low accelerating voltages.

The «Gentle Beam» system allows for the study of erythrocytes in blood smears without the deposition of conductive coatings and without damaging the objects under investigation for a time sufficient to make the necessary photographs [2].

Investigations of blood smears were carried out at accelerating voltages of 1 and 2 kV with a voltage applied to the investigated object of 8-10 V.

An experimental study of volunteer blood cells in vitro was also conducted. Blood, placed in a glass tube, was gradually cooled, and then warmed. During the cooling and heating, 6 blood smears were made alternately: immediately after venous blood sampling at a temperature of + 36.6 ° C; then at

temperatures of + 8.0 ° C; + 2.0 ° C; - 1.7 ° C; + 12.5 ° C and + 31.0 ° C. Blood sampling from deceased persons from hypothermia was made from the brain region where the temperature was maximum (from +6 ° C to 20 ° C) compared to other tissues and organs. The minimum temperature in the soft tissues of the upper and lower extremities was -40 ° C, in the lungs +12 ° C, in the liver +10 ° C.

**Results and discussion.** There is a problem of differentiation of the forms of acanthocytes and echinocytes, therefore in this work for the evaluation of erythrocyte species the results of other studies [3] were used, where the characteristic parameters of differentiation of different forms of erythrocytes and their association with diseases based on images obtained with the scanning electron microscope (SEM). Figure 1 shows the characteristic forms of erythrocytes - acanthocytes (A), echinocytes (E) and schizocytes (S).

Echinocytes have small identical protuberances distributed evenly, while acanthocytes are protuberances of various sizes and are unevenly distributed over the surface of the cell.

During the study of blood smears, REM images of erythrocytes were obtained for various causes of death. In Fig.2. images of red blood cells of a young man whose blood smear was made the day after his death are presented. Death occurred within 30 minutes as a result of a stab wound.

In the field of vision with an increase in 1000 times, the prevalence of dysmorphic erythrocytes is observed in comparison with normal ones. It should be noted that the dysmorphic erythrocytes are close in shape to the acanthocytes. Unchanging cells form small «coin pillars», and the modified cells are tightly connected to each other by processes. In this image, fragments of hemolyzed erythrocytes are not observed.

In Fig. 3 shows the erythrocytes of a man who died of a gunshot wound whose blood smear was made on the second day after the onset of death.

In the case of a gunshot wound, the changed erythrocytes are similar in form to acanthocytes. The same dysmorphic erythrocytes are also observed in Fig. 1 in the case of a stab wound wound. In contrast to Fig. 2 there are signs of hemolysis of erythrocytes, i.e. a small number of fragments of erythrocytes are seen, almost all cells form conglomerates. Unlike the first case, the amount of unchanged red blood cells is significantly less, which may be due to a temporary factor: in the second case, a smear was made on the second day after the onset of death, while in the case of a stab wound cut, a day later.

In Fig. 4 depicts images of red blood cells of a 25-year-old man who died from hypothermia. The blood was taken a day later.

In this figure, all the red blood cells are changed and most likely they can be attributed to echinocytes, and they are evenly distributed in one layer. In contrast to the previous images in this figure, it is observed that all red blood cells are interconnected very tightly and form small groups. The processes of erythrocytes in the frozen have a more acute form than those of the deceased from wounds, and also more evenly distributed over the entire surface of the erythrocytes.

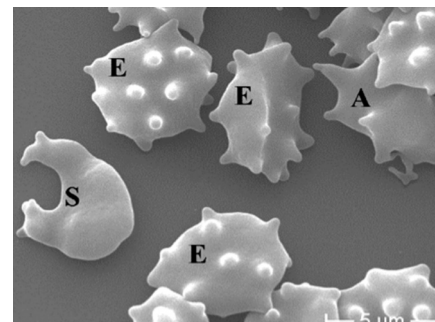


Fig.1. SEM images of erythrocyte forms

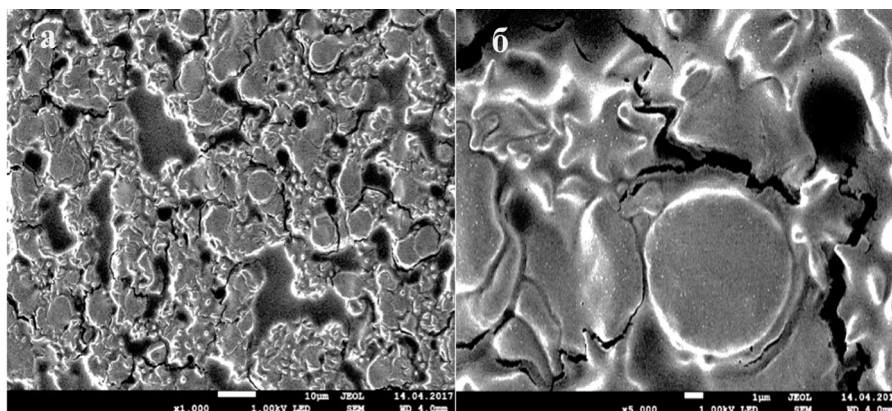


Fig.2. SEM images of erythrocytes died from a stab wound: a) with an increase of x1000, b) with an increase of x5000

In addition to studies of blood cells from cadaveric material, REM studies of blood cells of a young male volunteer were performed.

In Fig. 5-6 presents SEM images of erythrocytes of blood smears of a living healthy person on a slide, obtained at

various temperature effects on a blood sample.

The blood in the test tube was cooled gradually and as the cooling was carried out applying blood smears to the slide. Obviously, with positive blood temperature values (from + 36.6 °

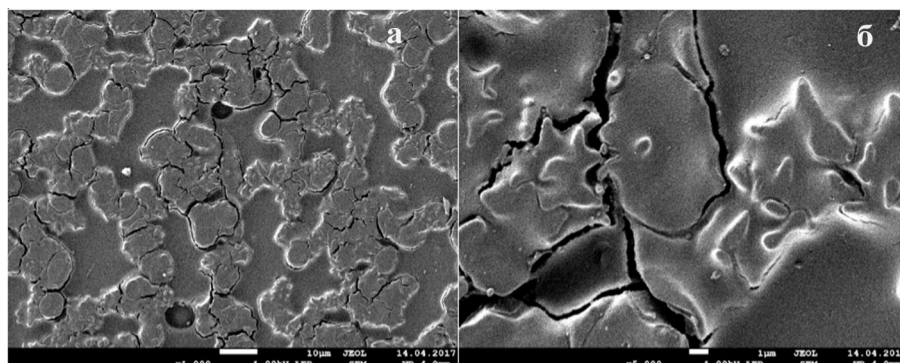
C to + 2.0 ° C), no significant changes in the morphology of erythrocytes are observed (Fig. 5). However, at a negative temperature (-1.7 ° C), dermorphic erythrocytes appear in a small amount in a form close to the acanthocytes (Figure 6), as well as a small number of schizocytes. In addition, the formation of coins and conglomerates of erythrocytes is observed. Then gradually the blood was heated. The REM images of erythrocytes obtained with the heating of blood do not differ from their images obtained after exposure to negative temperature.

The results obtained by us show that the appearance of certain forms of erythrocytes of cadaveric material depends on the causes of death. So, when dying from a stab-cut and gunshot wounds, erythrocytes take acanthocyte forms, and when undercooling, they take echinocyte forms.

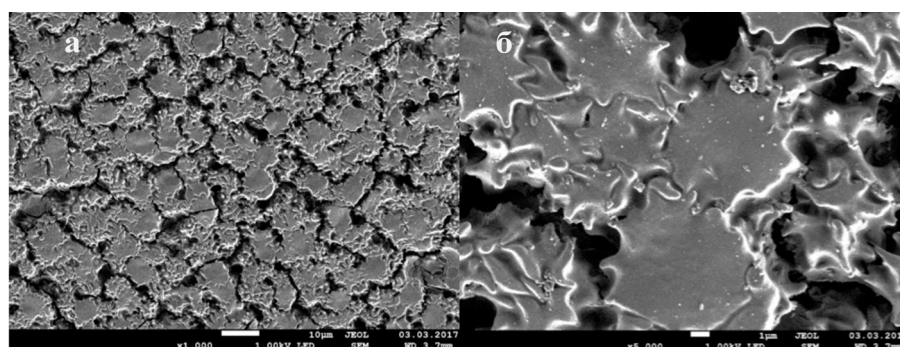
In the results of the experiment conducted in vitro, at small negative temperatures in SEM images, the appearance of acanthocytes is observed as in cases of death from wounds. In the deceased from hypothermia and other causes, blood samples were taken at approximately the same small positive temperatures. It should be noted that in the case of in vitro red blood cells did not change their forms up to a temperature value of + 2.0 ° C. This suggests that the appearance of acanthocytes in the blood of the deceased from hypothermia is possible only with prolonged stagnation of the corpse in a medium with a negative temperature, i.e. Provided that the temperatures of the internal vital organs decrease to negative values.

According to the results of this study, the comparison of dysmorphic erythrocytes during supercooling and cooling of blood samples in vitro shows that the mechanisms of the changes in the forms of red blood cells in these cases are different.

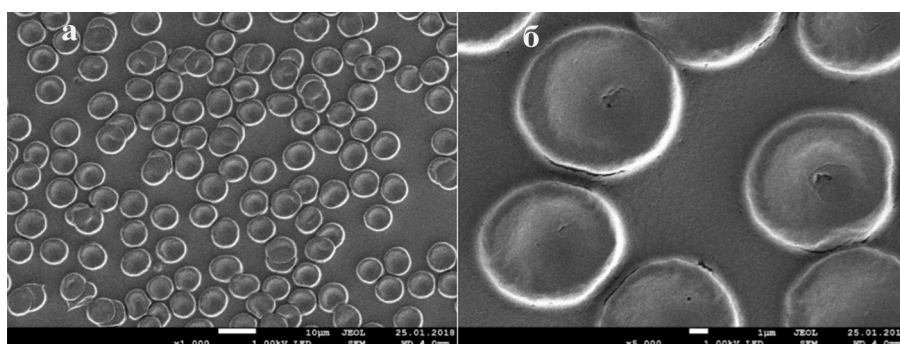
It is known that the acanthocyte forms of erythrocytes are determined by the defect of the structural membrane [4, 5], whereas the echinocyte forms can be induced and canceled by pH, osmolality, biochemical and even electrical changes [6-9]. Irreversibility of changes in the forms of acanthocytes is confirmed in experiments in vitro: acanthocytes, which appeared as a result of a drop in the temperature of the blood sample under study to negative values, do not disappear with and without an increase in the temperature of the blood in the field of view of SEM images. Unlike acanthocytes, erythrocytes of the echinocyte form, which are observed in persons who died from hypothermia, can



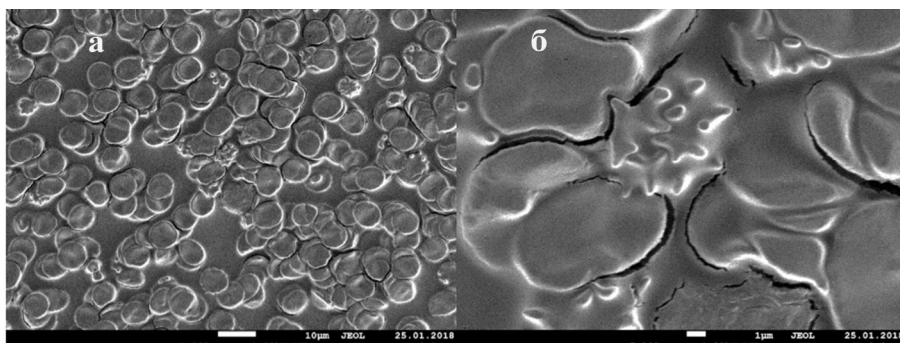
**Fig.3.** SEM images of erythrocytes died of a gunshot wound: a) with an increase of x1000, b) with an increase of x5000



**Fig.4.** SEM images of erythrocytes deceased from hypothermia: a) with an increase in x1000, b) with an increase of x5000



**Fig.5.** SEM images of volunteer erythrocytes at a temperature of + 2 ° C: a) with an increase of x1000, b) with an increase of x5000



**Fig.6.** SEM images of volunteer erythrocytes at a temperature of -1.7 ° C: a) with an increase of x1000, b) with an increase of x5000



be restored.

**Conclusion.** Thus, the results of the SEM study obtained by us indicate that the forms of erythrocytes in persons who died from various causes differ, namely, during overcooling - erythrocytes take echinocytic form, and when wounded - acanthocytic. This fact gives us the opportunity to assume that the process of dying during hypothermia has its own characteristics. It is necessary to further in-depth study of this pathology at the molecular-cellular level to find solutions to restore the body's vital activity in the first days after death from hypothermia.

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# GAMMA BACKGROUND ENVIRONMENT DURING MAGNETIC STORMS AND THE CONTENTS OF SODIUM AND POTASSIUM IN ERYTHROCYTES IN PATIENTS WITH ARTERIAL HYPERTENSION DEPENDING ON THE TEMPERAMENT AND ANTIHYPERTENSIVE THERAPY

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## ABSTRACT

Arterial hypertension is one of the major independent risk factors for complications of cardiovascular diseases, stroke, myocardial infarction, acute and chronic heart failure. In the structure of cardiovascular diseases arterial hypertension occupies the first position in disability and mortality of the working population. In recent years, this contributes to the growth of psycho-emotional stress, anxiety and depression. Periods of sharp changes heliometeofactors also combined with an increase in the proportion of individuals with complications of hypertension.

Thus, in the period of magnetic storms, there was an increase in gamma radiation power (within the regional norm), an increase in the degree of psycho-emotional stress and a change in the concentration of electrolytes in the blood of both healthy and persons with cardiovascular disease. The aim of the study was to establish the relationship between the dynamics of  $\gamma$ -background of the environment during magnetic storms and the content of potassium and sodium in red blood cells in patients with hypertension with different temperament and anxiety, taking options for antihypertensive therapy: targeted and not targeted (empirical) on the blockade of psychosomatic characteristics of patients, as well as to determine the most effective treatment option. The prevailing temperament - choleric, sanguine, phlegmatic and melancholy - was determined using the psychological test of John Eysenck and A. Belov, the presence and severity of depression - Je. Ahmetzhanov psychological tests. Potassium and sodium content in erythrocytes was determined by ion-selective method. The gamma background of the medium was measured using the dosimeter «Master».

It was found that the decrease in the activity of the sympathetic Department of the autonomic nervous system and the hypothalamic-pituitary-adrenal system (cortisol), and the increase in the activity of the renin-angiotensin-aldosterone system (aldosterone) in the temperamental series of choleric – sanguine – phlegmatic – melancholy was combined with a decrease in the level of oxygen utilization by tissues and potassium content in erythrocytes and an increase in sodium content in both healthy and patients. Compared with the empirical version of antihypertensive therapy, against the background of a targeted treatment option, the period of return of the values of the studied parameters, the level of oxygen utilization by tissues, the content of potassium and sodium in erythrocytes, as well as the degree of reaction of the body (according to the correlation analysis) were practically the same as in healthy individuals of the corresponding temperament, which indicates in favor of a higher efficiency of the treatment option targeted at the relief of psychosomatic features of the patient.

**Keywords:** hypertension, solar activity,  $\gamma$ -background, erythrocytes, potassium, sodium, correlation.

**Introduction.** Arterial hypertension (AH) is one of the major independent risk factors for development of complications of cardiovascular diseases [11, 13, 14]. Psychoemotional tension, anxiety and depression contribute to an increase in the proportion of people with AH complications in the modern world [1, 11]. The course of AH is closely related to sodium accumulation and potassium decrease in blood [13,14]. Periods of increased solar activity (SA) are also combined with changes in the electrolyte composition, rheological properties of blood and an increase in the proportion of persons with complications of hypertension [4, 5, 6, 16]. Studies have shown that magnetic storms (MS), as a consequence of changes in CA, are combined with changes in the concentration of electrolytes, as well as the trace element composition of blood (potassium, sodium, magnesium) in healthy and hypertensive patients [4, 5, 16]. However, no studies have been found on the relationship between the  $\gamma$ -background of the external environment in the MS period and the potassium and sodium content in erythrocytes (Er) in people taking different variants of antihypertensive therapy (AHT).

**Material and methods of research.** In the period from 1995 to 2017, 848 engineering and technical workers of men aged 44-62 years (average  $54 \pm 1.8$  years) were examined in the polyclinic, who were diagnosed with stage II hypertension (GB-II, degree 2, risk 3) in the cardiology Department. The disease duration averaged  $11.6 \pm 1.4$  years. The presence of essential hypertension was determined by the criteria set out in [13, 14]. 422 healthy men, compatible on the main anthropo-social indicators, served as control. The prevailing temperament – choleric (Ch) sanguine (Sg), phlegmatic (Ph) and melancholic (M) was measured using a psychological test [15] by 3 times testing before treatment (0) and after 3, 6, 9 and 12 months of AHT. The magnitude of reactive and personal anxiety was determined by [17]. Persons who scored  $32.0 \pm 0.6$  points, to high-anxiety (HA) from  $42.8 \pm 0.4$  points and above are referred to low-anxiety (LA).

The contents of potassium and sodium (mmol/l) in er were determined by ion-selective method on the apparatus "RAPIDLAB-865" (Bayer, UK) [8].

To determine the coefficient of utilization of oxygen by tissues (CUOT, %) account for the voltage of the oxygen ( $O_2$ ) in the blood (venous and venous arterIALIZATION) ( $pO_2$ , mm Hg. art.) according to the approved and approved procedure [8], as well as saturation (saturation) of hemoglobin (Hb) with oxygen ( $SAO_2$ , %), which was determined using the blood gas analyzer "STAT PROFILE. pHox". The content of Hb (g/l) was determined by hemoglobincyanide method on the device CFC-2 [8]. The content of  $O_2$  in the blood ( $CaO_2$ ) was calculated with the formula:

$$CaO_2 = 1.34 \times Hb \times SAO_2 / 100 + pO_2, \text{ mm Hg. art.} \times 0.0031,$$

where  $CaO_2$  – oxygen content in the blood (in 1 ml per 100 ml); 1,34 – Hufner constant; Hb – hemoglobin content in the blood (in g per 100 ml);  $SAO_2$ , % – saturation of Hb with oxygen (in %);  $pO_2$  – oxygen tension in the blood (in mm Hg. art.); 0,0031 – the coefficient of oxygen solubility according to Bunsen [8].

Blood sampling was performed from the cubital vein (in dry test tube without preservative) in the morning, fasting, before treatment. The calibration curve was obtained by measuring the optical density of standard sodium nitrate solutions with a concentration of 5 to 320  $\mu\text{mol}$ . All studies were conducted from 8.00 am to 10.00 am, on an empty stomach, before taking AHT.

Features of antihypertensive therapy. According to the method of Je.R. Akhmetzhanov [2] mild depression was observed only in high-anxiety phlegmatics (HA/Ph) and melancholy (HA/M). According to the conclusion of psychoneurologists they did not need inpatient treatment. Perfectionism choleric (HA/Ch) and sanguine (HA/Sg) received anxiolytic that 96% sibazon 2.5 mg in the morning and at night and HA/Ph and HA/M antidepressant that 96% coaxil 12.5 mg in the morning and at night (in 4% of cases the zolofit at 25 mg/day), except lowanxiety individuals [12]. Stud-

ies conducted by us using the criteria set out in [3] showed the prevalence of sympathetic (SNS) Department of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal system (GGNS, cortisol) in Ch and Sg, and parasympathetic (PSNS) Department of ANS with predominant activity of the renin-angiotensin-aldosterone system (RAAS, aldosterone) in Ph and M persons. Based on the differences above, AHT included drugs that have been approved by order No. 254 of the health Ministry of Russia dated 22.11.2004 «On approval of the standard of care for patients with arterial hypertension» [7, 12]: selective beta-adrenoblockers ( $\beta$ -AB), angiotensin converting enzyme inhibitors (aceis), diuretics (hydrochlorothiazide), cardiomagnyl. From  $\beta$ -AB patients in 96% of cases received metoprolol 200 mg/day (4% of its analogues), and LA/Ch and LA/Sg 100 mg/day) and hydrochlorothiazide: HA/Ch and HA/Sg 25 mg/day, and LA 12,5 mg/day. Of aceis patients in 96% of cases took enalapril 20 mg/day (in 4% of cases its analogues) + veroshpiron 100–200 mg/day (in 75% of cases), rarely (25%) and hydrochlorothiazide 25 mg/day, because the content of potassium in the blood have been lower than those of Ch and Sg. LA/Ph and LA/M were administered enalapril 10 mg/day + hydrochlorothiazide (hydrochlorothiazide) – 12,5 mg/day. All patients received Panangin 2 tab./day and cardiomagnyl on 1 tab./day. Since Ch and Sg patients differed from Ph and M patients PSNS Department of VNS, as well as the activity of the hypothalamic-pituitary-adrenal system (GGNS cortisol), they were prescribed in 96% of cases of  $\beta$ -AB + hypothiazid. Patients with phlegmatics and melancholy differed from h and with the prevalence of PSNS of the VNS Department and the predominant activity of the renin-angiotensin-aldosterone system (RAAS by aldosterone). In this regard, the latter was appointed in 96% of cases of ACEI + veroshpiron. All other treatment options are called empirical (EAHT). In order to exclude the installation (on the result) attitude to the study, the authors did not appoint AHT, but only determined the

temperament, anxiety and the presence of the accepted variant of AHT. The above variant of CAHT was successfully tested during vascular wall remodeling in patients with arterial hypertension [10].

The values of  $\gamma$ -background power ( $\mu\text{r/h}$ ) were obtained daily by measuring  $\gamma$ -background of workplaces (20 measurements, dosimeter «Master») from 8.00 to 10.00 and compared with the data of the Department of ionospheric-magnetic forecasting of the West Siberian Department of Hydrometeorology and environmental monitoring (Novosibirsk). Variations of  $\gamma$ -background power from 1995 to 2017 ( $7.6\text{--}16.8 \pm 0.4 \mu\text{r/h}$ ) did not exceed the permissible regional values.

The method of superimposed epochs was used in the work [9], which takes into account the days before the magnetic storm ( - ), in the period (0) and after the MB (+): -7 -6 -5 -4 -3 -2 -1 -0 - +1 +2 +3 +4 +5 +6- +7 accordingly. The results were processed by methods of variation statistics ( $m \pm m$ ) using a standard software package «Statistica 7.0» and parametric student t-test, as well as the calculation of the correlation coefficient (r) Pearson. Values at  $p < 0.05$  were considered statistically significant. The study was carried out in compliance with the provisions of the Helsinki Declaration on treatment and examination of people and approved by the ethics Committee of the Novosibirsk state medical University on 20.11.2009, Protocol No. 18.

**Results and discussion.** The data obtained during the study period showed that oxygen utilization by tissues (according to COUT) and potassium content in Er significantly decreased, and sodium concentration increased in the temperamental series HA(LA) Ch > Sg > Ph > M (according to CUOT and potassium) and HA(LA) Ch < Sg < Ph < M (according to sodium) (table. 1 – 3). Thus, in Er HA(LA) of the melancholic content of sodium was higher and potassium lower than that of others. Of the many factors that affect the utilization of oxygen and the content of electrolytes, the observed differences can be linked to the prevalence of the activity of the RAAS (aldosterone) and the parasympathetic section of VNS (index Kerdo and initial vegetative tonus) in the Ph and M compared with Sg and with individuals. The study showed a significant increase in the  $\gamma$ -background of the medium (within the regional norm) for the day (-1) before, and a return to the initial values on the (+4) day from the beginning of MS (table. 1). In the period of magnetic storms in healthy individuals and against any variant of AHT, all patients showed a significant decrease in the value of CUOT (%) and potassium content, but an increase in the concentration of sodium in er. In the groups of HA (LA) choleric these changes were recorded per day (-1), in the groups of HA (LA) sanguine in the first (0) day, and in the groups of HA (LA) phlegmatic and melancholic on the second day (+1) from the beginning of MS (table. 1). In the context of the above, we note that ionizing radiation, including  $\gamma$ -rays, contribute to the ionization and excitation of atoms and molecules, as well as the radiolysis of water to form active forms of oxygen. The consequence of oxidative stress is an increase in the permeability of cell membranes for electrolytes and a number of enzymes. The fact that the changes in Ch-individuals occurred a day before MS is consistent with the results of the study [18], which found an increase in  $\gamma$ -background of the medium a day before MS and is associated with an increase in the

Table 1

Dynamics of  $\gamma$ -background (ur/h) and the coefficient of utilization of oxygen by tissues (%) in HA individuals on the background of EAHT (E) and CAHT (C) in the days of magnetic storms during the study period over the study period from 1995 to 2017

Days	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	Beero
$\gamma$ -phone	8.5-8.50±0.01	8.46±0.01	8.46±0.01	8.41±0.01	8.41±0.01	8.41±0.01	8.41±0.01	8.78±0.01	8.80±0.01	8.65±0.01	8.70±0.01	8.59±0.01	8.47±0.01	8.62±0.01	8.49±0.01	8.58±0.007
E	34.3-34.7±0.06	35.0±0.07	35.0±0.07	35.0±0.06	35.0±0.05	33.6±0.04	32.1±0.05	31.6±0.06	31.2±0.06	32.3±0.07	32.6±0.06	33.7±0.05	35.2±0.07	35.3±0.07	35.0±0.06	33.8±0.01
C	36.1-36.5±0.05	36.2±0.06	36.2±0.06	37.0±0.07	37.0±0.06	36.3±0.07	35.0±0.06	34.8±0.07	34.6±0.06	35.2±0.06	36.3±0.07	37.7±0.06	35.8±0.05	38.0±0.08	35.9±0.07	36.4±0.01
Choleric	37.9-37.0±0.07	37.0±0.06	37.0±0.06	38.0±0.07	37.1±0.06	37.6±0.07	35.7±0.05	35.5±0.06	36.0±0.07	36.3±0.06	37.9±0.07	37.6±0.06	36.7±0.05	38.2±0.05	36.8±0.06	36.9±0.01
Zd	45-44	44	45	44	46	44	46	44	45	44	46	44	44	46	46	673
E	33.3-37.4±0.06	36.9±0.05	34.2±0.07	34.0±0.06	34.0±0.06	32.8±0.07	30.8±0.06	29.3±0.05	29.2±0.08	29.5±0.07	29.6±0.06	29.6±0.05	32.7±0.07	33.8±0.06	33.6±0.06	32.4±0.01
C	46-46	44	44	47	44	43	48	49	44	43	45	43	46	48	47	683
Sanguines	34.7-34.3±0.07	34.2±0.06	35.4±0.07	35.6±0.06	35.6±0.06	35.4±0.03	35.1±0.05	33.6±0.06	32.9±0.05	35.3±0.04	33.8±0.04	33.9±0.07	34.9±0.07	37.6±0.06	36.8±0.06	34.9±0.01
Zd	44-46	47	47	43	44	43	47	48	50	47	44	48	48	45	47	691
E	36.5-35.5±0.06	35.6±0.06	36.7±0.05	36.4±0.06	36.4±0.06	36.6±0.05	36.6±0.06	34.4±0.06	33.9±0.06	33.7±0.06	33.8±0.06	37.0±0.06	35.6±0.07	38.6±0.05	37.0±0.08	35.8±0.01
C	48-45	44	44	48	44	44	46	45	48	46	44	46	48	46	46	688
Phlegmatic	32.5-32.7±0.07	32.9±0.05	32.4±0.06	33.0±0.06	33.0±0.06	32.8±0.05	32.5±0.04	32.3±0.05	28.1±0.06	28.7±0.07	28.8±0.06	28.5±0.07	33.2±0.07	31.7±0.06	33.3±0.05	31.5±0.01
Zd	44-46	45	45	44	48	48	49	52	54	47	46	49	48	44	48	712
E	34.4-34.5±0.06	37.5±0.06	33.6±0.05	34.4±0.04	34.4±0.04	33.6±0.04	34.5±0.07	33.4±0.06	32.4±0.05	31.5±0.06	31.1±0.05	31.3±0.06	33.4±0.05	33.6±0.06	33.8±0.06	33.3±0.01
C	44-43	44	44	46	44	46	46	48	47	49	44	43	44	43	48	679
Phlegmatic	35.6-35.8±0.06	36.0±0.07	35.8±0.06	35.9±0.05	35.9±0.05	36.0±0.06	35.9±0.05	35.1±0.06	33.8±0.07	33.4±0.05	32.3±0.04	32.7±0.04	34.9±0.04	36.2±0.05	35.0±0.05	34.9±0.01
Zd	49-49	44	44	46	44	44	45	49	55	49	46	49	49	48	48	714
E	30.6-30.9±0.06	31.0±0.05	31.2±0.07	31.2±0.07	31.2±0.06	29.9±0.05	28.9±0.04	28.6±0.05	27.6±0.06	27.3±0.06	27.4±0.06	27.0±0.04	27.4±0.06	30.2±0.05	30.9±0.06	29.3±0.01
C	44-45	44	44	43	44	43	44	47	44	43	44	43	44	43	46	661
Melancholic	33.3-35.4±0.07	35.1±0.06	33.4±0.07	33.2±0.05	33.2±0.04	33.2±0.04	33.2±0.04	32.4±0.06	31.3±0.05	31.2±0.06	30.7±0.06	29.7±0.06	29.8±0.07	32.8±0.06	32.6±0.06	32.5±0.01
Zd	44-43	47	47	48	45	48	45	48	45	46	44	43	44	46	44	680
E	34.5-34.8±0.05	34.9±0.05	34.7±0.06	35.1±0.06	35.1±0.06	35.2±0.05	35.0±0.06	35.3±0.05	31.8±0.05	31.7±0.06	32.0±0.05	32.5±0.05	34.5±0.05	35.5±0.06	35.5±0.05	34.2±0.01
C	46-45	46	46	46	44	44	45	48	49	44	46	47	46	46	44	686

Note. Here and further: ZD-healthy persons; the denominator indicates the total number of examined

Table 2

Dynamics of  $\gamma$ -background (ur/h) and the potassium content in erythrocytes (mmol/l) in PΦ individuals on the background of EAHT (E) and CAHT(C) in the days of magnetic storms during the study period from 1995 to 2017

Days $\gamma$ -phone	-7-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	Beero
Choleric	8.5-8.50±0.01	8.46±0.01	8.45±0.01	8.41±0.01	8.45±0.01	8.70±0.01	8.78±0.01	8.80±0.01	8.65±0.01	8.70±0.01	8.59±0.01	8.47±0.01	8.62±0.01	8.49±0.01	8.58±0.007
	89.7-89.5±0.4	89.1±0.3	88.2±0.3	88.6±0.4	88.3±0.3	84.1±0.3	83.5±0.3	83.3±0.4	84.9±0.3	85.2±0.3	86.9±0.3	89.6±0.4	88.2±0.4	89.1±0.3	87.2±0.1
	44-45	44	44	48	43	49	48	46	47	44	43	44	43	45	677
	91.1-90.0±0.4	89.4±0.3	91.5±0.4	89.6±0.3	89.8±0.3	89.0±0.4	85.5±0.4	85.8±0.4	87.2±0.4	92.2±0.3	91.9±0.3	91.4±0.3	93.4±0.3	91.5±0.01	90.0±0.1
Sanguines	44-43	44	46	44	45	44	46	44	44	48	43	46	43	44	668
	91.4-89.9±0.4	89.3±0.4	91.0±0.4	89.8±0.4	89.4±0.2	87.4±0.3	86.6±0.4	85.9±0.3	86.2±0.4	91.6±0.4	91.2±0.4	90.9±0.4	92.5±0.3	87.9±0.3	89.9±0.1
	45-44	45	44	46	44	46	44	45	44	46	44	44	46	46	673
	88.1-88.0±0.4	88.3±0.3	86.8±0.4	87.3±0.3	87.0±0.4	87.1±0.3	84.2±0.4	82.0±0.5	81.7±0.4	81.9±0.3	84.8±0.4	86.8±0.3	87.8±0.4	88.2±0.3	86.0±0.1
Phlegmatic	46-46	44	47	44	43	48	49	44	43	45	43	46	47	47	682
	89.3-88.1±0.4	88.6±0.4	90.2±0.3	88.7±0.3	88.9±0.4	90.9±0.4	84.6±0.3	84.0±0.2	83.4±0.2	86.6±0.4	91.0±0.4	88.6±0.05	91.1±0.3	88.5±0.4	88.2±0.1
	44-46	47	43	44	43	45	48	44	46	44	46	48	45	46	690
	89.5-88.8±0.4	88.7±0.5	90.1±0.4	89.4±0.3	88.8±0.05	89.0±0.4	88.9±0.3	84.0±0.4	83.8±0.3	85.5±0.3	89.9±0.3	87.9±0.4	90.4±0.3	88.0±0.4	88.2±0.1
Melancholic	48-45	44	48	44	44	45	48	46	44	46	48	46	46	49	691
	86.8-88.4±0.4	88.0±0.4	85.4±0.3	86.0±0.4	85.8±0.3	85.7±0.4	85.1±0.3	81.9±0.3	80.0±0.3	80.2±0.3	83.0±0.4	83.9±0.4	84.1±0.04	86.0±0.4	84.3±0.1
	44-46	45	44	48	48	49	52	54	47	46	49	48	44	48	715
	89.4-89.0±0.4	87.7±0.3	88.4±0.4	87.0±0.3	85.8±0.3	87.9±0.2	85.2±0.4	82.7±0.3	82.2±0.3	82.1±0.5	82.9±0.3	86.0±0.4	89.7±0.4	86.3±0.5	86.3±0.1
	44-43	44	46	44	46	46	48	47	49	44	43	44	43	48	679
	89.1-88.7±0.4	89.7±0.4	89.7±0.5	90.3±0.4	90.0±0.4	90.2±0.3	89.2±0.4	86.8±0.4	82.5±0.5	83.0±0.4	85.3±0.5	90.4±0.4	88.7±0.3	90.4±0.4	87.9±0.1
	49-49	44	46	44	44	45	49	55	49	46	44	49	48	48	708
	85.5-85.3±0.3	85.0±0.4	84.0±0.3	84.6±0.3	84.5±0.4	84.3±0.3	82.3±0.5	82.0±0.3	81.2±0.3	80.0±0.4	80.0±0.5	82.5±0.4	84.5±0.6	85.3±0.6	83.4±0.1
	44-45	44	43	44	43	44	47	44	43	44	43	44	43	46	661
	86.7-86.6±0.3	86.9±0.3	87.2±0.3	86.7±0.4	86.9±0.3	87.3±0.4	87.0±0.4	81.0±0.4	81.1±0.3	83.0±0.4	83.7±0.3	86.5±0.4	87.6±0.3	86.2±0.4	85.6±0.1
	44-43	47	48	45	48	45	48	45	46	44	43	44	46	44	684
	86.9-86.2±0.3	86.0±0.4	86.7±0.4	86.0±0.3	86.2±0.05	87.7±0.4	86.7±0.3	81.6±0.4	81.3±0.4	81.1±0.3	83.3±0.4	86.3±0.3	87.3±0.4	87.1±0.3	85.4±0.2
	46-45	46	46	44	44	45	48	49	44	46	47	46	46	44	686

Table 3

Dynamics of  $\gamma$ -background (ur/h) and the content of sodium in erythrocytes (mmol/l) in HA individuals on the background of EAHT (E) and CAHT(C) in the days of magnetic storms during the study period from 1995 to 2017

Days $\gamma$ -phone	-7-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5	+6	+7	Beero
Choleric	8.5-8.50±0.01	8.46±0.01	8.45±0.01	8.41±0.01	8.45±0.01	8.70±0.01	8.78±0.01	8.80±0.01	8.65±0.01	8.70±0.01	8.59±0.01	8.47±0.01	8.62±0.01	8.49±0.01	8.58±0.007
	9.7-9.3±0.08	9.7±0.07	8.9±0.07	9.7±0.08	9.4±0.07	10.7±0.09	11.5±0.1	11.9±0.1	12.1±0.1	11.9±0.1	9.1±0.1	9.1±0.1	8.7±0.08	9.2±0.1	10.1±0.04
	44-45	44	44	48	43	49	48	46	47	44	43	44	43	45	677
	9.1-9.2±0.1	9.3±0.09	8.9±0.08	9.4±0.08	9.2±0.08	9.9±0.1	10.1±0.1	9.8±0.1	10.6±0.1	8.9±0.1	9.4±0.1	9.4±0.09	8.9±0.09	9.4±0.08	9.3±0.05
Sanguines	44-43	44	46	44	45	46	46	45	44	46	44	46	43	44	668
	9.0-9.1±0.07	9.2±0.06	8.6±0.08	9.2±0.09	9.0±0.06	9.6±0.08	9.9±0.07	9.9±0.06	9.6±0.07	8.8±0.08	8.6±0.09	9.2±0.1	8.5±0.1	9.1±0.07	9.2±0.06
	45-44	45	44	46	44	46	44	45	44	46	44	46	43	46	673
	10.8-10.9±0.1	11.1±0.08	10.6±0.09	10.8±0.09	11.0±0.09	10.9±0.08	12.6±0.08	13.3±0.1	13.5±0.1	13.2±0.1	12.8±0.1	11.2±0.08	11.0±0.07	11.0±0.08	11.7±0.05
Phlegmatic	46-46	44	47	44	43	48	49	44	43	45	43	46	48	47	682
	9.9-10.0±0.07	11.0±0.07	9.7±0.08	11.1±0.1	10.8±0.1	9.7±0.1	11.6±0.09	12.4±0.07	12.9±0.08	11.2±0.08	10.2±0.09	10.0±0.07	10.0±0.08	10.1±0.08	10.7±0.06
	44-46	47	43	44	43	43	48	50	47	44	48	48	45	47	690
	9.8-9.9±0.07	10.1±0.07	9.5±0.06	9.9±0.09	9.9±0.08	9.1±0.08	11.6±0.1	12.4±0.1	12.9±0.1	9.2±0.08	10.2±0.1	10.0±0.1	10.0±0.09	10.1±0.1	10.3±0.09
Melancholic	48-45	44	48	44	44	45	48	46	44	46	48	46	46	49	691
	11.7-11.5±0.1	11.5±0.1	11.8±0.08	11.3±0.09	11.5±0.07	11.6±0.1	12.0±0.1	13.7±0.1	14.0±0.09	14.3±0.08	13.3±0.1	11.8±0.1	12.0±0.09	11.8±0.1	12.3±0.07
	44-46	45	44	48	48	49	52	54	47	46	49	48	44	48	715
	10.6-10.9±0.08	11.3±0.09	10.8±0.08	10.9±0.08	11.0±0.09	11.1±0.07	11.1±0.08	12.8±0.1	13.5±0.1	12.3±0.09	12.0±0.09	11.3±0.008	9.9±0.07	10.8±0.07	11.4±0.06
	44-43	44	46	44	46	46	48	47	49	44	43	44	43	48	679
	10.5-10.8±0.07	11.1±0.06	10.7±0.06	10.6±0.06	10.9±0.09	11.0±0.09	11.2±0.07	12.6±0.06	13.4±0.06	13.0±0.09	12.8±0.08	11.8±0.09	10.8±0.08	11.5±0.07	11.5±0.05
	49-49	44	46	44	44	45	49	55	49	46	44	49	48	48	708
	12.8-13.0±0.08	12.5±0.07	13.3±0.07	12.6±0.06	12.8±0.09	13.0±0.09	13.6±0.08	14.9±0.07	14.9±0.06	15.0±0.07	14.4±0.08	14.1±0.09	13.2±0.09	13.1±0.08	13.6±0.05
	44-45	44	43	44	43	44	47	44	43	44	43	44	43	46	661
	11.7-11.9±0.09	12.1±0.08	11.6±0.09	11.7±0.09	11.8±0.09	11.7±0.09	12.0±0.08	13.1±0.09	14.3±0.08	14.6±0.07	13.8±0.06	12.1±0.08	12.1±0.1	11.9±0.08	12.4±0.04
	44-43	47	48	45	48	45	48	45	46	44	43	44	46	44	684
	11.6-11.8±0.08	12.1±0.09	11.4±0.07	11.5±0.07	11.6±0.08	11.4±0.1	11.8±0.1	12.8±0.01	14.2±0.1	14.4±0.09	13.9±0.09	12.0±0.08	12.0±0.08	12.0±0.1	12.3±0.04
	46-45	46	46	44	44	45	48	49	44	46	47	46	46	44	686



Table 4

Correlation coefficients between the dynamics of  $\gamma$ -background, CUOT, potassium and sodium content in erythrocytes during magnetic storms in high- and low-anxiety patients with AH-II with different temperament against the background of empirical (E) and targeted (C) AHT during the study period from 1995-2017

	CUOT, %						Potassium, mmol/l						Sodium, mmol/days					
	Highanxiety			Lowanxiety			Highanxiety			Lowanxiety			Highanxiety			Lowanxiety		
	Patient	Healthy	ChE	Patient	Healthy	ChE	Patient	Healthy	ChE	Patient	Healthy	ChE	Patient	Healthy	ChE	Patient	Healthy	ChE
ChE	-0.830±0.02	-0.477±0.01	-0.477±0.01	-0.45±0.02	-0.29±0.01	-0.29±0.01	-0.814±0.02	-0.447±0.01	-0.447±0.01	-0.48±0.01	-0.24±0.01	-0.24±0.01	+0.725±0.02	+0.420±0.02	+0.420±0.02	+0.47±0.02	+0.28±0.02	+0.28±0.02
ChC	-0.464±0.01	-0.474±0.01	-0.474±0.01	-0.27±0.01	-0.23±0.01	-0.23±0.01	-0.724±0.01	-0.454±0.01	-0.454±0.01	-0.49±0.01	-0.25±0.01	-0.25±0.01	+0.438±0.02	+0.456±0.03	+0.456±0.03	+0.46±0.03	+0.27±0.03	+0.27±0.03
SgE	-0.745±0.01	-0.474±0.01	-0.474±0.01	-0.27±0.01	-0.23±0.01	-0.23±0.01	-0.485±0.01	-0.482±0.01	-0.482±0.01	-0.43±0.01	-0.27±0.01	-0.27±0.01	+0.430±0.02	+0.470±0.03	+0.470±0.03	+0.28±0.03	+0.26±0.01	+0.26±0.01
SgC	-0.420±0.01	-0.474±0.01	-0.474±0.01	-0.27±0.01	-0.23±0.01	-0.23±0.01	-0.583±0.01	-0.463±0.0001	-0.463±0.0001	-0.25±0.01	-0.25±0.01	-0.25±0.01	+0.621±0.03	+0.470±0.03	+0.470±0.03	+0.27±0.02	+0.27±0.02	+0.27±0.02
PhE	-0.638±0.01	-0.394±0.01	-0.394±0.01	-0.37±0.01	-0.27±0.01	-0.27±0.01	-0.567±0.01	-0.436±0.01	-0.436±0.01	-0.37±0.01	-0.27±0.01	-0.27±0.01	+0.630±0.03	+0.386±0.02	+0.386±0.02	+0.38±0.02	+0.27±0.02	+0.27±0.02
PhC	-0.453±0.01	-0.469±0.01	-0.469±0.01	-0.25±0.01	-0.25±0.01	-0.25±0.01	-0.489±0.01	-0.489±0.01	-0.489±0.01	-0.28±0.01	-0.28±0.01	-0.28±0.01	+0.449±0.03	+0.386±0.02	+0.386±0.02	+0.25±0.02	+0.25±0.02	+0.25±0.02
ME	-0.585±0.01	-0.469±0.01	-0.469±0.01	-0.40±0.01	-0.25±0.01	-0.25±0.01												
MC	-0.365±0.01	-0.469±0.01	-0.469±0.01	-0.29±0.01	-0.25±0.01	-0.25±0.01												

concentration of radioactive radon gas on these days several times.

Against the background of EAHT, a significant return of the studied parameters to the baseline values in the groups of HA choleric was observed on (+4) day, sanguine on (+5), and HA phlegmatic and melancholic on (+6) day from the beginning of MS, and in the groups of LA persons on the day before: LA/Ch – Sg – Ph – M: +3 – +4 – +5 – +5 (table. 1 – 3). Against the background of CAHT, compared with the EAHT variant, the return to the initial values was recorded a day earlier: in the groups HA/Ch – Sg – Ph – M at +3 – +4 – +5 – +5, and in groups LA/Ch – Sg – Ph – M on: +2 – +3 – +4 – +4 day from the beginning of MS, respectively (table. 1 – 3). In contrast to the groups taking EAHT, against the background of CAHT, the terms of return of the studied parameters to the initial values approached those in healthy HA(LA) persons of the corresponding temperament (table. 1 – 3). The correlation analysis carried out on days using the method of superimposed epochs, between the change of  $\gamma$ -background and the content of potassium and sodium in Er during MS in patients, regardless of the variant of AHT, and in healthy individuals, established a reliable inverse correlation with the value of the CUOT and the concentration of potassium, but direct – with the content of sodium. But in the background, EAHT, correlation at the HA patients was high, and LA patients, the mean order of importance. On the background of CAHT in HA patients correlation was average, and in the groups of LA degree of importance, as well as in HA(LA) healthy individuals of the corresponding temperament (table. 4).

These studies have shown that between the increase in  $\gamma$ -background of the medium in the MS period, on the one hand, and the size of the CUOT, as well as the content of electrolytes in Er, on the other, there was a reliable relationship. Based on these data, already the day before the start and during the period of MS observed increase  $\gamma$ -background environment (within the boundaries of acceptable regional standards). And the first the day before the MS reacted the body sympathotonic choleric, and then the rest in the days of the MS and increase  $\gamma$ -background environment. It is unlikely to increase the activity of free-radical lipid peroxidation (SPOL) of membranes under conditions of increasing  $\gamma$ -background of the medium in the normal range. However, under the influence of these heliogeophysical fac-

tors (intense electromagnetic field of the Earth and an increase in  $\gamma$ -background of the medium), the obtained combination probably contributed to the development of a cascade of SPOL reactions, which resulted in an increase in the permeability of Er membranes and a decrease in magnesium [4, 16], potassium and CUOT values, but an increase in sodium concentration in Er. In contrast to the empirical AHT, against the background of CAHT, associated with a decrease in the activity of SNS in Ch and Sg and the activity of RAAS (aldosterone) in Ph and M patients, the degree of response (according to correlation analysis), as well as the coincidence of the timing of the return of the value of the CUOT and the electrolyte content to the initial values, plus less significant differences in the magnitude of changes in the CUOT and the content of the studied electrolytes in Er with those in healthy HA(LA) persons of the corresponding temperament, indicates in favor of greater efficiency of CAHT.

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## GENDER FEATURES OF PSYCHOEMOTIONAL STATUS IN CARDIOVASCULAR PATHOLOGY

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### ABSTRACT

The article analyzes the psycho-emotional state of persons with cardiovascular disease, depending on gender and the socio-hygienic factors. The study analyzed the results of 140 people with cardiological diagnosis of various etiologies in terms of situational and personal anxiety, depression, hostility, and aggressiveness. The psychodiagnostic examination included Beck Depression Inventory, State-Trait Anxiety Inventory, and Buss-Durkee Hostility Scale. Among the surveyed there were 68 women (mean age = 43.7 years) and 72 men (47 years). The analysis showed that at the age of 41 to 50 years we found the highest indicators of situational and personal anxiety, and aggression. Significant depressive symptoms are more often noted between the ages of 31 and 40 years. Among women we've found significantly higher rates of anxiety and depression. There were no significant differences in indicators of hostility and aggression. A combination of high hostility and low aggressiveness is noted, which indicates a tendency to contain and suppress aggressive manifestations and may be a predictor of psychosomatic pathology. The main social risk factors in cardiovascular pathology affecting the psycho-emotional state of the subjects include the level of education, dissatisfaction with the state of health, financial situation, nutrition, lack of proper diet and sleep disorders in the nature of their aggression.

**Keywords:** anxiety, depression, hostility, aggressiveness, cardiovascular diseases, gender.

**Introduction.** According to WHO, cardiovascular diseases (CVD) are the leading cause of death worldwide. The study of risk factors of these diseases receive great attention, among them a significant place is given to psychosocial factors. Researchers have found connection of CVD with affective disorders such as anxiety and depression, which most often have the nature of comorbidity [7 - 9, 13, 14]. Depression is considered an independent risk factor in the pathogenesis of CVD and can both provoke a somatic disease and also be a factor worsening the prognosis of cardiovascular events. It is noted that chronic emotional stress and socioeconomic status are interrelated and largely determine the integral risk of cardiovascular diseases [3]. Studying the phenomenon of hostility, J.C. Barefoot et al. confirmed that it is this trait that is stable over time and helps to predict cardiovascular and overall mortality, including that associated with high blood pressure [12]. Regarding the effect of hostility on CVD current research data are ambiguous and require additional testing.

**Research objective** - study of the gender characteristics of psycho-emotional status of persons with cardiovascular pathology.

**Materials and methods.** Within the framework of research at Yakut Science Center of Complex Medical Problems "Effect of Metabolic Syndrome to Development of Coronary Arteries Atherosclerosis Residents of Yakutia", a medical, social and psychodiagnostic examination of the population was conducted during field trips from 2013 to 2016 in different areas of the Sakha (Yakutia) Republic. A one-stage medical examination of the population was carried out with participa-

tion of a cardiologist, a neurologist, and a therapist. With the help of a questionnaire developed by the YSC CMP, data on the social status and living conditions of the population were obtained.

From the surveyed test data of 140 people with verified cardiological diagnosis were selected, of which 68 were women (48.6%) and 72 - men (51.4%). The age of the subjects ranged from 18 to 61 years. The average age of men was  $47 \pm 9.98$ , women –  $43.7 \pm 9.51$ . The ethnic composition of the selection was represented mainly by indigenous people – Yakuts -52.1% and low-numbered peoples of the North 25%, and other nationalities composed in total 22.9%.

For the psychodiagnostic study, the Beck Depression Inventory (BDI), the Spielberger-Hanin Scale of Situational (SA) and Personal Anxiety (PA) Scale (State-Trait Anxiety Inventory), and Buss-Durkee Hostility Scale, which differentiates aggression and hostility, have been used.

Statistical processing of the research results was carried out using the IBM SPSS Statistics 23 software package with the calculation of the Pearson correlation coefficient and significance of differences for independent samples – Student's *t*-test. The significance of the statistical differences was taken at a value of  $p < 0.05$ .

**Results and discussion.** The cardiovascular pathology in the examined group was mainly represented by hypertension - 72.8% of subjects, 5% were diagnosed with coronary heart disease and 22.2% - other CVD. The distribution of CVD in age groups showed that more than 70% of patients were in the range from 40 to 60 years.

Analysis of the psychodiagnostic examination data depending on age showed that high rates of SA (35.4%, of the number surveyed of the corresponding age) and PA (47.9%) are more often recorded between the ages of 41 and 50 years. Severe depressive symptoms occur between the ages of 31 and 40 years (29.4%). High rates of hostility were noted at the age of 18 to 30 years (43.7%), and aggressiveness in the period from 41 to 50 years (8.3%).

Among the entire examined high SA was registered in 25.7%, and moderate in 55% of respondents. High PA was noted in 40% of subjects, and moderate in 48.6% (Table 1). Depending on the gender, statistically significant differences were noted for SA ( $t = 2.19$ ,  $p = 0.03$ ) and PA ( $t = 2.77$ ,  $p = 0.006$ ) with the prevalence of indicators among women, which is consistent with the data of many studies.

Many authors note that the prevalence of anxiety in CVD is higher than depression rates. Thus, in the study of Antonysheva O.V. high SA was detected in 43.5%, and PA in 55.5% of persons with arterial hypertension (AH) [1]. In the work of Kiseleva M.G., it is indicated that in chronic CVD, outside the acute form, anxiety magnitude is 25% [5]. The data obtained by us, on average, correspond to the data of earlier studies and characterize a rather high frequency of PA among the studied group.

An analysis of correlations showed that with an increase in the level of SA & PA, there was a significant increase in the degree of depression ( $r = 0.40$ ,  $p < 0.01$ ;  $r = 0.53$ ,  $p < 0.01$ ), hostility ( $r = 0.19$ ,  $p < 0.05$ ;  $r = 0.27$ ,  $p < 0.01$ ), aggression ( $r = 0.18$ ,  $p < 0.05$ ;  $r = 0.22$ ,  $p < 0.05$ ).

Table 1

Distribution of anxiety levels among respondents, n (%)

Anxiety level	Both genders		Men		Women	
	SA	PA	SA	PA	SA	PA
Mild	27 (19.3)	16 (11.4)	15 (20.8)	11 (15.3)	12 (17.6)	5 (7.3)
Moderate	77 (55)	68 (48.6)	46 (63.9)	40 (55.5)	31 (45.6)	28 (41.2)
Expressed	36 (25.7)	56 (40)	11 (15.3)	21 (29.2)	25 (36.8)	35 (51.5)
Total	140 (100)	140 (100)	72 (100)	72 (100)	68 (100)	68 (100)

0.01). The increase in the level of SA & PA correlates with the level of education ( $r = -0.19$ ,  $p < 0.05$ ;  $r = -0.28$ ,  $p < 0.01$ ). High SA was also associated with poor nutrition ( $r = 0.24$ ,  $p < 0.05$ ), and PA with lack of employment ( $r = 0.17$ ,  $p < 0.05$ ).

In men, the increase in SA was associated with a low financial position ( $r = 0.32$ ,  $p < 0.05$ ), low nutrition rating ( $r = 0.32$ ,  $p < 0.05$ ), with frequent use of alcohol ( $r = 0.27$ ,  $p < 0.05$ ), and also negatively correlated with the number of children ( $r = -0.30$ ,  $p < 0.05$ ). Indicators of SA positively correlated with ethnicity, i.e. for the migrant population, high indicators were more characteristic ( $r = 0.31$ ,  $p < 0.05$ ); with age SA indices decreased ( $r = -0.27$ ,  $p < 0.05$ ). Among women SA had a negative correlation with ethnicity (high rates were more characteristic for the Yakuts ( $r = -0.24$ ,  $p < 0.05$ ); it also correlated with an increase in the level of education ( $r = -0.24$ ,  $p < 0.05$ ).

PA among women was also associated with the level of education ( $r = -0.27$ ,  $p < 0.05$ ); among men, no significant correlations were found.

Thus, in the structure of anxiety, the most significant social factors are low financial standing and the associated lack of nutrition, and among women - high level of education. In the studies of Gafarov V.V. it was noted that in women with higher and primary education with a high level of PA, there was a tendency to more frequent development of hypertension [10], which is also seen in our study, because our selection is dominated by individuals with hypertension.

Mild depression by the Beck Depression Inventory was observed in 27.9% of subjects, moderate depression - 19.3%, expressed - 12.8%, severe depression was not diagnosed (Table 2). According to literature data the frequency of depressive disorders at various cardiovascular pathologies varies from 18 to 60% [4]. Thus, according to the data of the "Coordinate" program in patients with hypertension severe depression occurs in 27.6%, an increase in the level of depressive disorders - in 52% of patients [6]. Our data, especially in men, are may be due to the fact that men ignore the experienced difficulties due to the assigned social role. In the case of gender distribution, significant differences were found in the studied groups, depression rates

were significantly higher among women ( $t = 2.39$ ,  $p = 0.018$ ), which also corresponds to the literature data.

The data of the correlation analysis showed that the increase in the degree of depression was associated with dissatisfaction with the state of health ( $r = 0.18$ ,  $p < 0.05$ ), low material position ( $r = 0.20$ ,  $p < 0.05$ ), and lack of nutrition ( $r = 0.19$ ,  $p < 0.05$ ) and a negative assessment of nutrition ( $r = 0.18$ ,  $p < 0.05$ ). In men, the degree of depression was associated with dissatisfaction with living conditions ( $r = 0.28$ ,  $p < 0.05$ ). Among women, the severity of depression correlated with a negative assessment of nutrition ( $r = 0.34$ ,  $p < 0.01$ ).

Thus, high rates of depression are more associated with low material well-being and the lack of nutrition associated with it.

According to the results of the Buss-Durkee Hostility Scale (Table 3), high hostility was noted in 23.6% of subjects, and aggressiveness in 4.3%, i.e. with a sufficiently pronounced hostility, aggressiveness is very low, besides that in more than half (58.6%) of the results of the subjects are at a level below the norm. Based on the fact that hostility is a cognitive-emotional component, and aggressiveness is more related to the emotional-behavioral component, it can be concluded that subjects with a negative attitude, dissatisfaction with the life situation cannot realize their aggressive tendencies due to excessive self-control and tendency to suppress negative feelings. The presence of negative attitudes towards the world without the possibility of their expression due to emotional control causes internal tension, which creates the basis of psychosomatic pathology.

Depending on gender among indicators of hostility and aggression, no significant differences were found ( $t_{\text{ns}} = -0.16$ ,  $p = 0.86$ ;  $t_{\text{ag}} = -2.16$ ,  $p = 0.16$ ). In their research Akimova E.V. [2] and Gafarov

Table 2

Distribution of depression levels among respondents, n (%)

Depression level	Both genders	Men	Women
Absent	56 (40)	36 (50)	20 (29.4)
Mild	39 (27.9)	15 (20.8)	24 (35.3)
Moderate	27 (19.3)	16 (22.2)	11 (16.2)
Expressed	18 (12.8)	5 (7)	13 (19.1)
Severe	0 (0)	0 (0)	0 (0)
Total	140 (100)	72 (100)	68 (100)

V.V. [10] revealed that the prevalence of hostility among men was 46.4%, and among women - 43.6%, in our study, the rates are lower, but also do not have significant differences depending on gender. Also in the study of S.H. Hosseini it was found that patients with arterial hypertension are characterized by the presence of anger as a personality trait, as well as its suppression [11], which also can be traced in our study.

High hostility was also associated with a low material position ( $r = 0.21$ ,  $p < 0.05$ ), and aggressiveness was correlated with smoking ( $r = 0.16$ ,  $p < 0.05$ ). High male hostility correlated with a short sleep duration ( $r = 0.39$ ,  $p < 0.01$ ), and aggression with late bedtime ( $r = 0.30$ ,  $p < 0.05$ ). Among women, high hostility was associated with low material status ( $r = 0.28$ ,  $p < 0.05$ ) and lack of employment ( $r = 0.26$ ,  $p < 0.05$ ), and aggression correlated with late awakening in the morning ( $r = 0.26$ ,  $p < 0.05$ ). Thus, aggressive tendencies in men were associated with a lack of sleep, and in women, on the contrary, with prolonged sleep, which most likely is derived from a lack of employment.

**Conclusions.** Among the studied women, significantly higher rates of situational, personal anxiety and depression were found; there were no significant differences with regard to hostility and aggression.

In the study group, there were high rates of hostility combined with low aggressiveness, that may indicate the propensity of the subjects to suppress negative feelings, increased emotional control, which can lead to an accumulation of psychological stress and may be a predictor of psychosomatic pathology.

Main social risk factors in cardiovascular pathology affecting the psycho-emotional state of the subjects include the level of education, dissatisfaction with the state of health, financial situation, nu-

Table 3

Hostility and aggressiveness levels, n (%)

Level	Both genders		Men		Women	
	HS	AG	HS	AG	HS	AG
Below average	11 (7.8)	82 (58.6)	6 (8.4)	39 (54.2)	5 (7.3)	43 (63.2)
Average	96 (68.6)	52 (37.1)	50 (69.4)	29 (40.3)	46 (67.7)	23 (33.8)
Above average	33 (23.6)	6 (4.3)	16 (22.2)	4 (5.5)	17 (25)	2 (3)
Total	140 (100)	140 (100)	72 (100)	72 (100)	68 (100)	68 (100)



trition, lack of diet and sleep disorders in the structure of aggression.

It is necessary to conduct additional research, taking into account the etiology and pathogenesis of cardiovascular diseases, as well as considering a wider range of risk factors.

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## COMPARATIVE STUDY OF REPARATIVE REGENERATION OF THE ORAL MUCOSA IN EXPERIMENT

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### ABSTRACT

At present, treatment of inflammatory-destructive diseases of the oral cavity is still a relevant problem. Despite the fact that any dentist disposes a wide range of medical preparations, it is difficult to choose one with the least amount of complications. While managing elderly patients with dental problems the goal is not only to facilitate healing of the oral mucosa, but also to prevent the recurrence of pathology. Injections of platelet autoplasm may be useful in treatment of inflammatory-destructive diseases of the maxillofacial region. Injections of platelet autoplasm for inflammatory-destructive diseases of the oral mucosa, effect of synergism of this method in combination with other therapeutic means justify the need for further study of this issue. In this work, in order to study the regenerative potential, the simulated wound defect in the oral cavity of 30 dogs was treated experimentally. Regeneration control, treatment and supervision lasted 14 days alongside with application of various pharmacotherapeutical methods. To exclude additional factors which might affect the final result of the experiment associated with individual physiological features, study of experimental local treatment methods was carried out within one body: traditional methods of treatment; application of Tysol composition with L-arginine; injections of platelet autoplasm were included in the treatment plan as well as a combined method of treatment. Platelet autoplasm injections combined with Tizol applications with L – arginine was proved to help restore and heal the oral mucosa much faster comparing to other treatment methods.

**Keywords:** regeneration, experiment, dogs, platelet autoplasm, Tizol, pain, hyperemia, wound, treatment.

**Introduction.** Works on modeling and research into regeneration potential of oral cavity wounds can be seen both in domestic and foreign sources being reflection of the fundamental aims of the research. [11]. Experiments provide the possibility of a deeper research into pathogenetic mechanisms of oral cavity diseases, substantiation of efficacy and directivity of new approaches to stimulation of the regeneration potential in the oral cavity without affecting the patient [12]. At present, there are some publications on experimental works to study regeneration potential of oral cavity tissues. This trend became popular mainly in surgical practice. Works on predictability of the oral mucosa healing (OMH) are associated with the principle of guided tissue regeneration. So, K.A.Aksenov et al. (2011) carried out an experiment on mini-pigs of Svetlogorsk breed making a model of wound process to study the process of surgical wounds regeneration in the oral cavity after their suturing and to increase efficacy of treatment in surgical dentistry clinics. This article reflects necessity to change the approach to the final stage of surgical interference - suturing for positive result of treatment. [1].

To substantiate experimentally application of recombinant epidermal growth factor, an experiment on white Wistar rats was performed. On the hard palate of laboratory animals wounds of 5 mm in diameter were made as deep as to the bone. Healing progress under immunodeficiency conditions against the

background of recombinant growth factor therapy was evaluated planimetrically, pathomorphologically and histologically. The research proved a favourable effect of the carried out therapy on the wound healing against the background of immunodeficiency [2].

In therapeutic dentistry application of electrochemically activated solutions for comprehensive treatment of erosive ulcerous OMH lesions in patients with lichen ruber planus was experimentally explored to study the character of epithelization. Experiments were performed on chinchilla rabbits. The authors studied effect of electrochemically activated solutions on activity of antioxidant defense enzymes in the rabbit's isolated erythrocytes *in vitro*. Laboratory data of the rabbit's blood proved the effect of electrochemically activated solutions on the activity of antioxidant defense which depends on oxidation-reduction potential of the solution possessing electron-donor properties [3].

The problem of developing new highly effective methods of OM diseases is still pressing and important in therapeutic dentistry. Therefore, these are experimental studies that help obtain necessary data on efficiency of pathogenetic impact of new medical compositions and methods of therapy directed to stimulate reparative regeneration in the oral cavity prior to their clinical testing.

As alternative inflammation [6] prevail in the pathogenesis of inflammatory-destructive geriatric diseases and lead to

destruction of the oral mucosa [5], at present researches are done into modern and effective methods of therapy restoring reparative regeneration of the damaged tissue [7].

In spite of the fact that medical science advances with seven-league strides and dentists possess accumulated experience, the issue of research into reparative process of the oral mucosa remains pressing [8]. This is the reason for further advanced researches into peculiarities of reparative regeneration of oral mucosa in order to enhance clinical efficiency of treatment and patients' quality of life.

These are platelets that release different growth factors which enhance healing of regenerative potential. Fibroblasts, in turn, produce collagen, hyaluronic acid and elastin. This process results in formation of young connective tissue. Growth factors also block osteoclasts and stimulate osteoblasts proliferation, thus suppressing bone loss and promoting its regeneration [9].

The data obtained with clinical researches substantiate therapeutic effect of PRP – therapy. Including injections of platelet autoplasm into the treatment plan, the researchers managed to reduce or eliminate inflammatory parodontal diseases, prevent and arrest bone destruction, enhance local immunity of the oral cavity and normalize oral microflora [4,10]

At present, PRP – therapy is performed either with injections or applications. Following centrifugal separation regime is

an important integral part of the method [4]. At the same time application of this method for inflammatory-destructive diseases of the oral mucosa, efficiency of PRP-therapy synergism in combination with other therapeutic methods prove the necessity of further studies of the issue.

**Objective of the study:** Experimental evaluation of wound defect healing process in dogs' oral cavity in conditions of application of a new combined method and traditional plans of treatment.

**Material and methods of the research.** In the experiment, clinical evaluation of a standard wound defect in dogs' oral cavity was performed which helped qualitatively evaluate dynamics of the wound healing against the background of therapy. The study was performed in the laboratory of pathology modeling of SBI "Volgograd Center of Medical Sciences". The experiment was performed on 30 male dogs weighing from 2 to 16 kg, living in a vivarium ( $t^{\circ} = 22-24^{\circ} \text{C}$ , relative air humidity 40-50%), with a natural regime and standard diet (GOST P 50258-92), following rules of laboratory practice while carrying out pre-clinical researches in the Russian Federation (GOST 3 51000.3-96 и 1000.4-96) as well as rules of humane treatment of animals (Report of the AVMA Panel on Euthanasia JAVMA, 2001) and International recommendations of European convention for Protection of Vertebrate Animals in experimental researches (1997). Experiments were approved by the Ethical Review Committee of the Volgograd State Medical University (Proceedings No 2036).

The animals were premedicated by 0.1% atropine injected in the left gastrocnemius muscle in the amount corresponding to the animal's weight (under the producer's instructions). Anesthesia was performed with "Zolitel-100" injected intramuscularly in the amount of 8 mg/kg (under the producer's instruction). When the animal stopped reacting to stimulation, it was immobilized with a device used for immobilization of the experimental animal for sampling bioptic material from the oral cavity (Patent No 62527 of 10.06.2016).

Teeth of the immobilized animals were cleaned with ultrasound, dental deposits were removed manually, oral mucosa was treated with antiseptic solution of 0.05% chlorhexidine bigluconate to eliminate a bacterial factor which could affect the course of experiment.

Experimental modeling of the pathological process was performed by making lesions on the oral mucosa of the

upper and lower jaw, left and right from premolar 1 in the vestibule of the oral cavity. Four wounds 1x1 cm each were made on the mucosa.

The operation was performed under intravenous anesthesia by Zoletil and wounds made with a scalpel and pincers.

To exclude additional factors associated with individual physiological characteristics which could affect the final result of the experiment, research into experimental methods of local treatment was performed on one body.

Group 1 (control) – On the right lower jaw the dogs' OM wound was treated with a traditional method (application of Celestoderm: Solcoseryl= 1:1).

Group 2 (experimental) – On the right upper jaw applications of Tizol with L-arginine were used for the complex treatment of OM wound defect;

Group 3 (experimental) – On the left upper jaw the treatment plan included injections of platelet autoplasm;

Group 4 (experimental) – On the left lower jaw 2.0 ml of platelet autoplasm was administered into the OM wound defect by infiltration along the mucobuccal fold alongside with application of Tizol with L-arginine composition using sandwich-technique.

Platelet plasma was made by taking 7 ml of venous blood from the laboratory animals with a butterfly syringe into a vacuum test-tube. The test-tube was put into the centrifuge 80-2S (China) at 3 500 rpm for 5 min. With this method 3.5 ml of platelet autoplasm was obtained.

Subsequently, the wound defect was treated by injecting platelet autoplasm into the lesion.

The wound defect condition in the animals was clinically monitored daily for 2 weeks.

Hyperemia level was evaluated using clinical evaluation scale: 0 - no hyperemia, 1 point – insignificant hyperemia, 2 points – moderate hyperemia, 3 points – marked hyperemia. Edema of the wound edges was also evaluated using 4-point scale: 0 – no edema, 1 point – insignificant edema, 2 points – moderate edema, 3 points marked edema. Area of the wound defect, OM regeneration index and OM regeneration intensity were determined using the technique developed by L.N. Dedova and I.N. Fedorova (2005), with the help of our device to measure the lesion area in the oral cavity (RF Patent for useful model No 66417 of 07.11.2016). The results were considered on the 3d, 7<sup>th</sup> and 14<sup>th</sup> day of treatment and monitoring. Photo documentation Dynamics of OM wound defects treatment in experi-

mental animals was photo documented with a Sony digital camera (8 megapixel). During experiment 480 photos were analyzed.

The data obtained were processed using the variational –statistical method, a PC and Microsoft Excel program for MS Windows XP /Microsoft Corp., USA, as well as Stat Soft Statistica v6.0. application package (A.P. Kulaichev, 2006) in accordance with standard methods of medical statistics. Statistical analysis was done using the method of variational statistics by determining mean (M), its mean error ( $\pm m$ ), evaluation of significance of differences by group with Student's test (t). Difference between compared indicators was considered to be significant with  $p < 0,05$ ,  $t \geq 2$  (V.I.Sabanov, E.R.Komina, 1996, I.F.Sprace et al. , 2006).

**Results and discussion.** Morphometric examination of the wound defect in the oral cavity against the background of treatment showed neither complications nor side effects in all groups, positive results were obtained in all groups, though healing dynamics was different depending on therapy conducted. So, edema decreased more rapidly in the 4<sup>th</sup> group of dogs whose treatment plan included a combined method of treatment (platelet autoplasm injections in combination with Tizol and L-arginine applications). On the 3d day edema indicators in the 4<sup>th</sup> group were  $1,5 \pm 0,09$  points which was 1.8 times less comparing with group 1 ( $2,7 \pm 0,08$  points); 1.5 times less comparing with group 2 (Tizol with L-arginine applications) and 1.4 times less comparing with group 3. This difference was statistically significant ( $p < 0,05$ ). Significant difference was also obtained on determining this indicator in groups 2 and 3 relative to the group with conventional treatment ( $p < 0,05$ ). The difference between group 2 and 3 was statistically insignificant ( $p > 0,05$ ). A week after the experiment began a slight edema was noted in the first three groups: group 1 –  $1,8 \pm 0,13$  points; group 2 –  $1,3 \pm 0,07$  points; group 3 –  $1,1 \pm 0,11$  points. In group 4 edema was estimated as  $0,3 \pm 0,08$  points, that indicates absence of edema in the dogs' oral cavity.

Differences between experimental groups relative to group 4 were also statistically significant ( $p < 0,01$ ), so, it can be noted that applying a combined method of wound treatment there is a clear tendency towards marked decrease of edema against the background of the treatment conducted. On the 14<sup>th</sup> day of the experiment all dogs on all four sides showed no signs of edema in the oral cavity.



Significant difference was also obtained on evaluation of hyperemia in the oral cavity. On the 3d day, hyperemia was  $2,53 \pm 0,19$  points in the group with conventional method of treatment which was 10% higher than in group 2 and 3 ( $2,3 \pm 0,05$  points with  $p > 0,05$ ) and 58% significantly higher comparing with the group with treatment of platelet autoplasm injections combined with Tizol and L-arginine applications ( $1,6 \pm 0,09$  points,  $p < 0,05$ ).

On the 7<sup>th</sup> day signs of hyperemia decreases in all groups. Significant difference was noted in group 4 comparing to other experimental groups ( $p < 0,05$ ). Hyperemia in group 4 was  $0,5 \pm 0,09$  points which was significantly 3 times lower comparing with group 1 ( $1,5 \pm 0,09$  points), 2.6 times lower comparing with the group whose treatment plan included applications of Tizol with L-arginine, and 2.4 times less comparing with group 3. Between groups 1,2 and 3 no significant difference was noted ( $p > 0,05$ ) on evaluation of indicators of hyperemia in the oral cavity. On the 14<sup>th</sup> day hyperemia in the dogs' oral cavity was not noted.

On the 3d day significant decrease of the wound defect diameter was noted, though in the group with combined method of treatment the diameter was  $4,6 \pm 0,12$  mm which was 34.7% lower comparing with group 1 with diameter of  $6,2 \pm 0,18$  mm which was 13% less comparing with group 2 ( $5,2 \pm 0,14$  mm and 15% less comparing with the group whose treatment plan included platelet autoplasm injections ( $5,3 \pm 0,15$  mm). Groups 2 and 3 showed significant difference relative to group 1 ( $p < 0,05$ ). The area of the wound defect also significantly decreased in all groups comparing with previously obtained data. It must be stressed that regeneration of the oral mucosa in the first three groups correspond to the 2<sup>nd</sup> degree of regeneration, and in the group with combined method of treatment the course of reparative processes was much more effective, degree III of the regenerative potential being the evidence.

A week after dynamic monitoring and treatment of the dogs the area of the wound defect significantly decreased in all groups, though in group 4 the postoperative wound was not visually revealed, its area was  $0,8 \text{ mm}^2$ . In the group with conventional method of treatment the area of the wound defect was  $8,7 \text{ mm}^2$ , that was 2.4 times significantly higher comparing with group 2 ( $3,59 \text{ mm}^2$ ) and 3.3 times higher comparing group 3 ( $2,57 \text{ mm}^2$ ), with  $p < 0,05$ .

After 14 days the wound defect disappeared in all four groups, no signs of inflammation were noted, the oral mucosa of all dogs fully regenerated.

### Conclusions.

Thus our experiment revealed that Tizol with L – arginine applications arrests inflammation much quicker in comparison with conventional therapy that is proved by significantly obtained difference on determining quantitative criteria. There was no significant difference between this group and the group where injections of platelet autoplasm were applied which proves the advantage of these two methods comparing with the conventional therapy and efficacy of both methods to enhance regeneration of the oral mucosa.

In spite of the fact that after 2 weeks full regeneration of the connective tissue in the oral cavity was noted in all dogs, in the group with combined method of treatment there is a tendency towards more marked and earlier epithelization, which is proved by significant difference in all periods of the experiment. One can suppose that injections of platelet autoplasm alongside with applications of Tizol with L-arginine more effectively influence the process and healing comparing with other methods of therapy.

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## EXPERIMENTAL PHYTCORRECTION OF ACUTE D-GALACTOSAMINE HEPATITIS IN WHITE RATS

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### ABSTRACT

The aim of our research was in defining hepatoprotective properties of new complex plant supplement on a rat model of D-galactosamine hepatitis. The new complex drug supplement is a dry extract consisting of *Hypocoum erectus* L., *Hedysarum dauricum*, *Glycyrrhiza uralensis* Fisch., *Calendula officinalis* and *Scutellaria baicalensis*. Intensity of the main pathogenetic syndromes was evaluated by biochemical tests, lipid peroxidation grade and morphological research. The use for the complex extract resulted in correction of functional state of the liver, inhibition of cytolysis and cholestasis, delay of LPO and enhancing synthetic function of liver manifested in albumin and fibrinogen increase.

**Keywords:** acute experimental hepatitis, hepatoprotective drugs, complex drug of medicinal plants.

**Introduction.** A necessity in finding new hepatoprotective drugs and supplements is dictated by the growing demand: increasingly widespread liver pathologies tending to chronic forms being caused by viruses, toxic agents including some medication [8, 9, 10]. Under these conditions, medicinal plants are of interest considering the wide range of their therapeutic effect, low toxicity and the possibility of gaining amplified effect by combining active components of complex plant supplements [1- 4].

The aim was in determining pharmacotherapeutical effectiveness of new complex medicinal supplement on a rat model of acute D-galactosamine toxic

hepatitis.

#### Materials and methods of research.

The researched plant supplement is a dry extract consisting of dry extracts of *Hypocoum erectum* L.; Papaveraceae grass, dry extract from *Hedysarum alpinum* L.; Leguminosae grass, dry extract of *Glycyrrhiza uralensis* Fisch.; Leguminosae roots, dried flower extract of *Calendula officinalis* L.; Compositae and dry root extract of *Scutellaria baicalensis* Georgi; Lamiaceae in proportion of 5:5:4:4:2.

Compounded preparations were performed using HPLC with UV-detector on MiLiChrom A-02 by ECONOVA (Милихром А-02, Эконова), Novosibirsk, Russia with column ProntoSIL-

120-5-C18 AQ (2 × 75 mm, Ø 5 µm; Meitron AG, Herisau, Switzerland); mobile phase: 0.2 M LiClO<sub>4</sub> with 0.006 M HClO<sub>4</sub> (A), MeCN (B). During the separation process profile of gradient elution was set to 0–40' 5–100% B, 40–43' 100% B with speed of 100 µl/min, temperature set to 35°C with UV-detection at a wavelength of 210 nm. Concentration of substances was measured with commercially available samples (Sigma-Aldrich). Detected components included: glycyrrhizic acid 2.06 ± 0.04%, baicalin 1.85 ± 0.04%, protopin 1.09 ± 0.03%, mangipyrin 0.68 ± 0.02%, typhaneoside and narcissin combined 0.27 ± 0.01%.

The pharmacotherapeutical effective-

ness of complex plant supplement was studied after inducing acute hepatitis in rats by D-galactosamine infusion. The chosen model of acute liver damage is known to be close to viral hepatitis in its morphological and biochemical features [5].

D-galactosamine was injected intraperitoneally in dose of 400 mg/kg [5]. The researched supplement was injected intragastrically in doses 100 (group 1), 200 (group 2), 300 (group 3) mg/kg one hour before D-galactosamine injection and then daily for 14 days. *Carsil* (*Silibinin*) obtained from the milk thistle plant *Silybum marianum* (L.) Gaertn. was used as a reference agent in a dose of 100 mg/kg daily likewise. Control group of white rats was injected with D-galactosamine but instead of pharmacological agents received an equal volume of distilled water. Intact group received only distilled water.

Functional state of the liver was evaluated by biochemical markers: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), cholesterol, total protein (reagents "Abris" and "Vital" on analyser "VitaRay"). Lipid peroxidation intensity was determined with Malondialdehyde (MDA) and conjugated dienes in serum [7]. In order to analyze the morphofunctional state of liver a set of histological, histochemical and histoensymological methods was applied [5].

The pharmacotherapeutical effectiveness of complex plant supplement was studied on 7th, 14th and 21<sup>st</sup> days of experiment. Data were analyzed using MedCalc version 18.5 statistical software [10]. Values were considered statistically

significant when  $P < 0.05$ .

**Results and discussion.** The use of D-galactosamine model did not cause acute lethality in experimental animals. General condition, reaction and mobility, appetite of the rats remained intact. There was no weight loss during first 7 days of the experiment in D-galactosamine groups while the animals of the intact group have gained 20-25 g.

Biochemical tests performed on D-galactosamine-exposed groups demonstrated drastic changes of the functional state of the liver (Table 1). A significant deviation of biochemical parameters was observed in the groups of rats with D-galactosamine-induced liver toxicity pointing to the development of the main pathogenic syndromes of liver damage: cytolysis, cholestasis, mesenchymal inflammatory reaction combined with hypoalbuminemia and hypocoagulation. The intensity of lipid peroxidation was evaluated by malondialdehyde and diene conjugates concentration in blood serum of the experimental animals [9] wherein in the experimental groups signs of lipid peroxidation were significant.

On the 7th day of the experiment in the control group of the animals activity of AST and ALT was amplified by 3,1-3,3 in comparison with the intact animals testifying to the expressed cytolysis that had developed from an early date. Albumin concentration was decreased by 14,9% (down to 31,4-34,0 g/l in 6 rats of the control group) reflecting remarkable change in the functional state of hepatocytes while the level of total proteins remained on the same levels due to globulin fraction growth. Furthermore, level of fibrinogen and prothrombin index dropped by

18,9% and more (Table 1).

In the comparison group (*Carsil*) on the according dates ALT and AST decrease was 7,32-10,25%. In the groups of rats receiving the studied plant supplement there was a more pronounced decrease of the activity of aminotransferases.

The degree of cholestasis severity was measured by complex evaluation of cholesterol concentration, ALP activity and GGTP in blood serum. As it is known, lipid metabolism values in rats' serum are lower than in human serum due to the functions of  $\alpha$ -muricholic, and  $\beta$ -muricholic acids that force cholesterol metabolism [9]. However, despite that fact in the experiment cholesterol level was still slightly growing because of the liver damage. In the comparison group on the 7th day of the trial ALP activity and GGTP level dropped by 9-10%. As a result of using the complex drug supplement a decrease in cholesterol levels was more compelling than a decrease of it in the comparison group (Tab. 1). Additionally a decrease by 17,5-18,5% of ALP and GGPT was demonstrated in the tested drug supplement group. Furthermore in the group of the drug supplement in dose 200 mg/kg demonstrated more substantial decrease in ALP, GGTP and cholesterol levels (in 6 out of 8 animals). In the given period of the experiment after injection with the studied supplement relevant suppression of peroxidation intensity manifested in a decrease of malondialdehyde and diene conjugates concentration by 18-24%

Pathomorphological study showed that in liver of animals from the control group on the 7th day of the observation after injection with D-galactosamine

**Table 1**

**Blood serum biochemical markers dynamics in D-galactosamine induced liver damage on rat model on the 7th day of the experiment ( $M \pm m$ ,  $n=8$ )**

Markers	Intact group	Groups with D-galactosamine induced liver damage				
		Control+ H <sub>2</sub> O	Comparison group + <i>Carsil</i>	Group 1 + 100 mg/kg complex supplement	Group 2 + 100 mg/kg complex supplement	Group 3 + 100 mg/kg complex supplement
ALT, U/l	58.6 $\pm$ 5.4	152.9 $\pm$ 9.2	141.7 $\pm$ 9.7	132.6 $\pm$ 8.2	123.5 $\pm$ 7.9*	125.4 $\pm$ 6.9
AST, U/l	73.5 $\pm$ 4.7	242.7 $\pm$ 10.2	217.8 $\pm$ 11.4	205.7 $\pm$ 9.1*	198.5 $\pm$ 11.3*	203.3 $\pm$ 9.2*
Cholesterol, $\mu$ mol/l	1.82 $\pm$ 0.13	3.52 $\pm$ 0.19	3.05 $\pm$ 0.12	2.97 $\pm$ 0.13	2.63 $\pm$ 0.14*	2.90 $\pm$ 0.12
ALP, U/l	308 $\pm$ 21	742 $\pm$ 41	667 $\pm$ 43	612.0 $\pm$ 27	604.7 $\pm$ 25*	619 $\pm$ 21*
GGTP, U/l	7.13 $\pm$ 0.31	23.94 $\pm$ 2.10	21.83 $\pm$ 1.34	19.45 $\pm$ 0.89*	19.75 $\pm$ 0.94*	18.38 $\pm$ 1.25
Albumin, g/l	42.5 $\pm$ 2.2	33.5 $\pm$ 1.4	37.3 $\pm$ 2.1	38.5 $\pm$ 1.3*	39.2 $\pm$ 1.2*	38.9 $\pm$ 1.7*
Total protein, g/l	72.9 $\pm$ 3.9	64.3 $\pm$ 2.4	64.5 $\pm$ 4.1	65.7 $\pm$ 3.8	68.7 $\pm$ 3.9	66.7 $\pm$ 2.1
Globulin, g/l	30.4 $\pm$ 2.9	30.8 $\pm$ 1.7	27.2 $\pm$ 2.6	27.2 $\pm$ 2.1	29.5 $\pm$ 1.9	27.8 $\pm$ 2.1
Fibrinogen, g/l	2.43 $\pm$ 0.13	1.51 $\pm$ 0.11	1.82 $\pm$ 0.19	1.97 $\pm$ 0.12*	2.03 $\pm$ 0.14*	1.99 $\pm$ 0.11*
Prothrombin index (PI) %	84.4 $\pm$ 4.7	50.3 $\pm$ 2.4*	57.1 $\pm$ 3.7	59.9 $\pm$ 2.9*	64.7 $\pm$ 3.8*	63.8 $\pm$ 3.4*

Note. In the Tables 1-2 \* - the differences are statistically significant between the control and experimental groups at  $P < 0.05$ ; n is the number of animals in the group

changes, characterized by dystrophic and necrobiotic transformation of hepatocytes, mesenchymal-inflammatory effect coupled with activation of macrophages, accumulation of lymphocytes in portal tracts and deterioration of bile tract cells were present. The use of the complex drug supplement in doses from 100 mg/kg to 300 mg/kg and the comparison drug Carsil had limited the grade of necrobiotic processes and mesenchymal-inflammatory effects induced by D-galactosamine. Thus, in the observation group on the 7th day moderate granular degeneration of hepatocytes prevailed. In the group of dose 100 mg/kg hepatocytes affected by hydropic dystrophy accounted for 2/3 of periportal lobe while in other drug supplement groups fractions of transformed hepatocytes were scarce and situated periportal. The data of morphometric research demonstrated that number of necrotic hepatocytes was lower in 1,9 times in average (compared to the data of the control group).

On the 14th day of the experiment after D-galactosamine-induced damage the animals demonstrated weight loss in comparison with the intact group by 7-10%, lowered appetite and moveability. Biochemical parameters reflected persistence of the main features of liver damage in experimental animals. After injection with Carsil a remarkable decrease of amynotransferases was observed.

During the second week of the experiment signs of cholestasis were still apparent. As a result of injection with the complex drug supplement ALP, GGTP and cholesterol were lower than that of the comparison group: the group of the studied supplement demonstrated de-

crease in ALP by 15,2% in dose 100 mg/kg and by 17,84% in the group of the dose 200 mg/kg while in Carsil group ALP was decreasing by 9,16%. On the 14-th day of the experiment hypoalbuminemia in the groups of the studied supplement was significantly less expressed than in the control group while coagulation parameters were normalizing as a result of increased synthetic ability of the liver. The grade of lipid peroxidation was decreasing.

On the 14-th day of the observation in animals' liver of the control group the expression of structural changes decreased in comparison to the previous control point. Dystrophic hepatocytes were found locally but not diffusely. In three specimens of the control group moderate hydropic dystrophy was still observed. In liver of the animals from experimental groups was observed moderate expansion of sinusoidal spaces, local venocapillary erythrostasis, increased blood filling of some vessels and granular degeneration of hepatocytes. Hepatocytes with lipid degeneration were scarce in the several portal tracts. In the results of morphometric research the number of fatty transformed hepatocytes was 5 times lower than that of the control group. As a result of delayed destruction of hepatocytes in the experimental groups significant signs of reparation were observed. Thus, in the group of studied supplement injected in dose 100 mg/kg and in the comparison group was found increased number of hypertrophic hepatocytes and binucleate hepatocytes (by 22%), while in groups with doses 200 mg/kg and 300 mg/kg the increase was 31% in comparison with the control group.

On the 3rd week of the experiment in the control group deviation of biochemical markers was less evident than that of the intact animals with ALT and AST close to those of the intact group. At the same time in the groups treated with the studied plant supplement relevant decrease in cholestasis was observed. The pathomorphological study of the specimens taken on the 3rd week of the trial showed no insignificant deviations.

**Conclusion.** After experimental D-galactosamine induced liver damage use of the comparison drug influenced the pathological processes by decreasing cytolysis and cholestasis on the 2nd week of the experiment while levels of albumin and globulin and parameters of coagulation remained constant. The use of the studied complex plant supplement had led to decrease of biochemical markers deviations. The grade of cytolysis in the experimental group №2 (dose of the complex drug supplement 200mg/kg) was significantly lower starting from the first control point (7 days after the beginning of the experiment) with ALT and AST dropping by 15-18% compared to the comparison drug at 7-10%. Based on the complex evaluation of cholesterol, ALP and GGTP levels the experiment had shown that the use of the drug supplement leads to significant growth of albumin, fibrinogen and prothrombin index levels evident of the improvements in synthetic function of the liver starting from the first point of the control. The use of the studied plant supplement contributed to a decrease in lipid peroxidation, inhibited the accumulation of malonaldehyde and diene conjugates with significant differences observed in the early periods of the experiment, on

Table 2

**Blood serum biochemical markers dynamics in D-galactosamine induced liver damage on rat model on the 14th day of the experiment (M±m, n=8)**

Markers	Intact group	Groups with D-galactosamine induced liver damage				
		Control+ H <sub>2</sub> O	Comparison group + Carsil	Group 1 + 100 mg/kg complex supplement	Group 2 + 100 mg/kg complex supplement	Group 3 + 100 mg/kg complex supplement
ALT, U/l	58.6±5.4	128.2±6.9	116.7±5.3*	103.6±5.4*	104.1±5.8*	105.1±4.9*
AST, U/l	73.5±4.7	207.0±9.4	189.7±7.1*	172.9±8.7*	169.9±8.3*	170.5±8.2*
Cholesterol, μmol/l	1.82 ±0.13	2.97±0.16	2.52±0.11*	2.44±0.15*	2.41±0.14*	2.43±0.15*
ALP, U/l	308±21	585.5±25	532.4±17*	496.5±18*	481.5±24*	497.7±17*
GGTP, U/l	7.43±0.31	18.82±0.8	16.31±0.7*	15.8±0.82*	15.43±0.72*	15.15±0.76*
Albumin, g/l	42.5±2.2	35.3±1.7	38.8±1.9	40.9±1.2*	40.5±1.1*	41.8±1.3*
Total protein, g/l	71.8 ±3.9	66.2±2.9	67.3±4.7	68.8±3.8	71.8±5.6	70.9±3.7
Globulin, g/l	29.34±2.9	30.9±3.7	28.5±2.8	27.9±2.1	31.3±1.4	29.1±2.1
Fibrinogen, g/l	1.93±0.11	1.97±0.11	2.05±0.10	2.51±0.12*	2.47±0.13*	2.53±0.12*
Prothrombin index (PI) %	84.4±4.7	50.3±2.4	57.1±3.7	59.9±2.9*	64.7±3.8*	63.8±3.4*



the 7th and 14th days of the observation.

Combined with ability to inhibit lipid peroxidation and apparent limitation of dystrophic and necrobiotic signs and lowered inflammatory intensity, improved reparation was observed. Consequently, the researched complex drug supplement demonstrated pronounced hepatoprotective effect in D-galactosamine-induced liver damage. Dose elevation to 200 and 300 mg/kg did not lead to the significant improvement.

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**CLINICAL CHARACTERISTICS OF  
ALCOHOLIC LIVER DISEASE**

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**ABSTRACT**

The features of the clinical course of alcoholic liver disease in various ethnic groups were studied in comparison with chronic alcohol-viral and viral hepatitis B.

All patients underwent clinical and laboratory examination.

It was revealed that in indigenous patients chronic alcoholic hepatitis was formed in a shorter time, as evidenced by the high frequency of their detection in the age groups up to 20 and from 20 to 29 years and was characterized by more pronounced clinical manifestations.

The main distinguishing features of alcoholic liver damage, regardless of the presence or absence of CVH infection, are hepatomegaly, the prevalence of pronounced extrahepatic manifestations, increased activity of AIAT in combination with GGT, and immunological changes.

**Keywords:** alcoholic liver disease, chronic alcoholic hepatitis, alcoholic viral hepatitis, chronic viral hepatitis B.

**Introduction.** Alcohol abuse has a complex negative effect on the human body, especially on the liver. Alcoholic liver disease (ALD) is manifested by alcoholic steatosis, acute and chronic alcoholic hepatitis, as well as alcoholic liver cirrhosis [1, 2, 4, 5, 6]. Development of ALD is also facilitated by excessive body weight and obesity, hepatopathy virus infection and immune factors [6, 7].

**Purpose of the study-** to study the features of the clinical course of alcoholic liver disease in different ethnic groups in comparison with chronic alcohol-viral and viral hepatitis B.

**Materials and methods of research.** Groups of patients with alcoholic hepatitis (84), alcoholic viral hepatitis (72), chronic viral hepatitis B (30) were examined. All patients underwent clinical and laboratory examination.

**Results of the study.** In 84 patients with chronic active alcoholic hepatitis (ACH), clinical syndromes and symptoms were analyzed in comparison with patients with viral-alcoholic hepatitis (AVH) and viral hepatitis B (CVH-B). Comparative characteristics of clinical manifestations of chronic hepatitis of alcoholic, alcoholic-viral and viral etiology are presented in Table 1.

Asthenic-vegetative syndrome was observed at ACH in 94,6%, at AVH in 90,3% and at CVH-B in 75,3% of patients, and with pain - 98,1%, hepatomegaly - 100%, dyspeptic disorders - 66,6% at patients of two compared groups.

Splenomegaly was observed in patients with ACH - 1.6 (1.9%), AVH - 2 (2.8%), CVH-B - 2 (6.6%). At alcoholic hepatitis, splenomegaly was determined only by ultrasound examination. Asthenic-vegetative syndrome, hepatomegaly occurred in practically all patients of the observed groups. At the same time, pain syndrome, dyspepsia disorders and systemic lesions were much more often de-

tected in patients with ACH and AVH.

Hemorrhagic syndrome was detected in ACH, AVH and CVH-B, respectively, in 25 (30.0%), 26 (36.4%), 10 (32.9%) patients, without significant differences in groups. Jaundice was more often observed in the ACH 18 group (21.4%) than CVH-B 4 (13.3%).

Hepatic signs in the compared groups were encountered in isolated cases. Extrahepatic systemic manifestations were significantly more often detected in alcoholic and alcohol-viral liver lesions compared with viral hepatitis (13.3%) (Table 2).

Systemic lesions were detected at ACH in 78 (92.9%), AVH in 51 (70.8%) and at CVH-B in 4 (13.3%) patients. In indigenous people at ACH systemic manifestations occurred in 53 (67.9%) and AVH - in 35 (68.6%), in non-indigenous patients ACH in 29 (37.2%) and AVH - in 8 (15.6%) respectively. In indigenous patients at ACH and AVH, the frequency of systemic manifestations was much higher than in the non-indigenous.

The gastric lesion in the form of chron-

ic gastritis was observed in 34 (40.5%), pancreatic damage - chronic pancreatitis, more often calcifying in 28 (33.3), lesions of salivary glands in the form of mumps in 21 (25.0%), kidney damage 25 (29.7%) - alcoholic nephritis or pyelonephritis, in 14 (19.4%) heart disease - alcoholic cardiomyopathy with heart failure, quite often with arrhythmia in 16 (19.0%). Lung bronchitis with a protracted clinical course was observed in 7 (8.3%) patients. The Raynaud syndrome was found in isolated cases at ACH and CVH-B. A moderate variant of the disease occurred in 82 (97.6%) patients with ACH, in 43 (59.7%) - AVH and in 17 (56.7%) CVH-B; frequent clinical symptoms were not severe hepatomegaly in patients of viral and alcoholic-viral etiology, a more pronounced increase in the liver was noted at alcoholic chronic hepatitis, together with systemic lesions, as well as pain, dyspeptic and asthenic-vegetative syndromes. A significant clinical variant of the disease was found at ACH in 2 (2.4%), AVH in 8 (11.1%) and at CVH-B in 5 (16.7%) patients (Table 3). At chronic viral hepatitis

**Table 1**

**Comparative characteristics of clinical manifestations of CH  
of alcoholic, alcohol-viral and viral etiology**

Clinical signs	Number of patients in groups with the presence of signs					
	ACH n – 84		AVH n – 72		HVG-B n – 30	
	%	n. persons	%	n. persons	%	%
Asthenic-vegetative	79	94.6±3.0	65	90.3±3.5	22	75.3±8.1
Dyspeptic	56	66.6±6.3	56	77.8±4.5	11	38.4±8.8
Painful	83	98.1±1.8	57	79.2±4.9	15	49.3±9.1
Hepatomegaly	84	100	71	98.6±1.4	29	97.3±3.3
Splenomegaly	2	1.9±1.8	2	2.8±1.9	2	6.6±4.6
Hemorrhagic	25	30.0±6.1	26	36.4±5.7	10	32.9±8.6
Jaundice	18	21.4±5.5	13	18.0±4.5	4	13.3±6.2
Hepatic signs:	14	16.6±4.9	7	9.7±3.5	1	3.3±3.3
a) Vascular asterisks	5	5.9±3.4	3	4.2±2.4	1	3.3±3.3
b) palmar erythema	9	10.7±3.8	4	5.5±2.7	-	-
Systemic damage in total:	78	92.9±3.4	51	70.8±5.4	4	13.3±6.2
Clinical variants of CH:						
moderately severe	82	97.6±1.8	68	94.7±2.7	25	82.2±6.8
severe	2.0	2.4±1.8	4	5.3±2.7	5	17.8±6.8

Table 2

**Comparative characteristics of systemic lesions in patients with chronic hepatitis of alcoholic, alcoholic-viral and viral etiology**

Clinical signs	Number of patients with the presence of signs in groups					
	ACH n-84		AVH n-72		HVG- B n-30	
	n	%	n	%	n	%
Systemic damage in total:	78	92.9±3.4	51	70.8±5.4	4	13.3±6.2
Lymphadenopathy	2	1.8±1.8	1	1.4±1.4	3	10.0±5.5
Fever	12	14.3±4.4	3	4.2±2.4	1	3.3±3.3
Articular syndrome	22	26±5.1	18	25.0±5.1	3	10.0±5.5
Skin syndrome	7	8.3±3.0	7	9.7±3.5	1	3.3±3.3
Renal damage	25	29.7±5.8	9	12.5±3.9	1	3.3±3.3
Heart Attack	16	19.0±4.9	14	19.4±4.7	1	3.3±3.3
Lung infection	7	8.3±3.0	2	2.8±1.9	1	3.3±3.3
Stomach lesion	34	40.5±6.7	25	34.7±5.6	-	
Pancreas lesion	28	33.3±6.5	29	40.3±5.8	-	
Lesion of the salivary glands	21	25.0±5.6	15	20.8±4.8	1	3.3±3.3
Raynaud's syndrome	3	3.6±1.8	-		1	3.3±3.3
Nodular periarteritis	-		-		1	3.3±3.3

B in the clinical picture, systemic lesions with unexpressed hepatomegaly manifested themselves more vividly.

Thus, in the majority of patients with chronic alcoholic hepatitis, systemic lesions were observed at moderately severe variants, and in patients with viral

hepatitis - severe variants of the disease.

At studying laboratory indicators (Table 4) at ACH, AVH and viral hepatitis, it turned out that 100% of patients showed hyperaminotransferase, more often than 5 and 10 times higher than normal, but higher than 10 times only in isolated

cases. An increase in the level of alkaline phosphatase was noted in 26 (31.0%) in patients with alcoholic chronic hepatitis (ACH), with AVH and CVH-B significantly less. Hypoalbuminemia was observed in 19 (22.6%) patients with ACH, in 9 (12.2%) AVH and in 2 (6.6%) CVH-B.

Hypergammaglobulinemia was noted in a small number of patients in all 3 groups. A significant increase in gamma-glutamyltranspeptidase (GGTP) was observed in patients with ACH, statistically significantly differed from those of the CVH-B group, and an increase in GGTP was noted in patients with AVH. Hypocholesterolemia was observed only in patients with chronic hepatitis B 16 (54%). Hypercholesterolemia was detected mainly in patients with alcoholic hepatitis. Anemia was more frequent in patients with alcoholic and alcohol-viral hepatitis. Leukopenia, leukocytosis and an increase in ESR occurred in isolated cases. From the laboratory indicators more characteristic for alcoholic hepatitis were hypoalbuminemia, increased activity of gamma-glutamyltranspeptidase and

Table 3

**Clinical variants of chronic hepatitis in different ethnic groups**

Clinical option	Number of patients in ethnic groups																	
	ACH						AVCH						CVH-B					
	indigenous n=53		non-indigenous n=31		total n=84		indigenous n=45		non-indigenous n=27		total n=72		indigenous n=21		non-indigenous n=9		total n=30	
	aбс.	%	aбс.	%	aбс.	%	aбс.	%	aбс.	%	aбс.	%	aбс.	%	aбс.	%	aбс.	%
Latent							3	6.7±3.7	18	66.7±9.1	21	29.2±5.4	3	14.3±7.6	5	55.6±16.6	8	26.7±8.1
Moderately severe with systemic manifestations	53	100.0	29	93.5±5.1	82	97.6±1.8	35	77.8±6.2	8	29.6±8.8	43	59.7±5.8	14	66.7±10.3	3	33.3±15.7	17	56.7±9.0
severe			2	6.4±5.1	2	2.4±1.8	7	15.5±5.4	1	3.7±3.6	8	11.1±3.7	4	19.0±8.6	1	11.1±10.5	5	16.7±6.8

Table 4

**Comparative analysis of laboratory parameters in patients with alcoholic, alcoholic-viral and viral etiology**

Indicator	Number of patients in groups					
	ACH n-84		AVCH n-72		CVH- B n-30	
	n	%	n	%	n	%
Hyperbilirubinemia (more than 20. 5 μmol / l)	21	25±5.5	5	6.8±3.0	4	13.7±6.2
Increase in the level of aminotransferases in total:	84	100	72	100	30	100
including less than 5 times	46	54.7±6.6	32	44.5±5.9	14	46.7±9.1
5 to 10 times	38	45.2±6.6	39	54.1±5.9	15	50.0±9.1
over 10 times	-		1	1.4±1.4	1	3.3±3.3
Increase in the level of alkaline phosphatase	26	31.0±6.1 <sup>x2,3</sup>	4	5.4±2.7 <sup>x1</sup>	2	6.6±4.6 <sup>x1</sup>
Hypoalbuminemia (less than 32g.l)	19	22.6±5.6 <sup>x3</sup>	9	12.2±3.9	2	6.6±4.6 <sup>x1</sup>
Hypergammaglobulinemia	3	3.6±5.0	3	4.2±2.4	1	3.3±3.3
Gammaglutamyltranspeptidase	80	95.2±3.0 <sup>x3</sup>	61	84.7±4.2 <sup>x1</sup>	1	3.3±3.3 <sup>x1,2</sup>
Rheumatoid factor	-		-		1	3.3±3.3
Positive LE-cell test	-		-		1	3.3±3.3
Hypocholesterolemia	3	3.6±5.0 <sup>x3</sup>	1	1.4±1.4 <sup>x3</sup>	16	54.0±9.1 <sup>x1,2</sup>
Hypercholesterolemia	57	67.8±6.2 <sup>x3</sup>	40	55.5±5.9 <sup>x3</sup>	1	3.3±3.3 <sup>x1,2</sup>
Thrombocytopenia	1	1.2±1.8	1	1.4±1.4	1	3.3±3.3
Anemia	19	22.6±5.6 <sup>x3</sup>	23	31.9±5.5 <sup>x3</sup>	1	3.3±3.3 <sup>x1,2</sup>
Leukopenia	4	4.7±3.0	2	3.1±1.9	2	6.6±4.6
Leukocytosis	1	1.2±1.8	-		-	
Increased ESR	4	4.7±3.0	-		1	3.3±3.3



hypercholesterolemia.

**Conclusion.** Thus, at chronic alcoholic hepatitis, the presence of extrahepatic systemic lesions is due to the toxic effect of alcohol on the endocrine glands, vessels, nervous system, and organs of the gastrointestinal tract, which was observed by other researchers. However, in indigenous patients they developed early and their number and severity were significantly higher [1, 5, 7].

Pain syndrome in patients with chronic alcoholic hepatitis in most cases is associated with the development of concomitant secondary chronic pancreatitis, gastritis and duodenitis. A number of authors have noted the presence of these diseases as the cause of the onset of pain. Chronic hepatitis combined with clinical symptoms is closer to alcoholic than to viral hepatitis. Very important was the fact that CVH replication markers were absent in all patients [2, 3, 6].

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**D.K. Garmaeva, M.T. Buzinaeva, A.I. Pavlova**

## MORPHOLOGY OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) OF LARYNX IN GENERAL HYPOTHERMIA

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#### ABSTRACT

We have studied the cytoarchitectonics of mucous-associated diffuse lymphoid tissue (MALT - mucosa-associated lymphoid tissue) of the larynx in persons who died from hypothermia. The material was collected in the summer (June, July, and August) and winter (December, January, and February) seasons of the year with the support from the State Budget Institution of the Bureau of Forensic Medical Examination of the Sakha (Yakutia) Republic. Death caused by low natural temperature occurred most often at ambient air temperatures ranging from -34°C to -40°C, less often at -31°C to -33°C. As one of the most frequent factors contributing to the onset of death from hypothermia is alcohol intoxication, for comparative characteristics of the morphology of lymphoid tissue, we also investigated the group of persons who died from general hypothermia with underlying alcohol intoxication.

Significant changes in the cellular composition of the mucous-associated diffuse lymphoid tissue of the larynx were revealed: a decrease in T- and B- lymphocytes and plasma cells and an increase in the number of destructively altered cells and macrophages.

**Keywords:** mucosa-associated diffuse lymphoid tissue (MALT), larynx, cytoarchitecture, hypothermia.

The study of the effects of low temperatures on the human body is one of the topical areas of basic and clinical medical sciences. The Sakha (Yakutia) Republic is a region with extreme climatic and geographical conditions, where the cold is one of the main environmental factors of adverse effects on the human body [1, 2, 5]. When activating protective reactions of the organism, an important role belongs not only to the central organs of the immune system, but also to its peripheral structures, in particular the immune (lymphoid) tissue of the walls of hollow organs. Located on the border between the external internal bodily en-

vironments, the peripheral parts of the immune system provide sanitation to the tissue complex. Destroying foreign substances and detoxification of the body [6, 13] depends on the functional activity of these structures.

When a person adapts to the conditions of the North, the mucosa-associated lymphoid structures of the respiratory organs are primarily affected by low temperatures, as they are the first "target" in the path of cold air penetration. In this regard, one of the promising areas of research on the pathological influence of the cold factor on the human body is the study of the immune structures of the

larynx, which are located at the surface of the organ and are the first specific barrier to the penetration of antigens, in particular cold air.

In both domestic and foreign scientific literature, there is zero data on the morphology of the mucosa-associated lymphoid tissue of the laryngeal walls related to death from general hypothermia, as well as when this type of death is combined with alcohol intoxication under conditions of low air temperatures in the Sakha (Yakutia) Republic. The purpose of our study is to optimize the postmortem diagnosis of death from general hypothermia by examining the cellular com-

position of the mucosa-associated diffuse lymphoid tissue of the laryngeal mucosa in the climatic conditions of the Sakha (Yakutia) Republic.

**Materials & Research Methods.** The material for the study was samples of the mucous membrane of the larynx from the region of the vestibule, the left and right ventricles and the sub-vocal region. The object of the study was diffuse lymphoid tissue of the mucous membrane of the larynx, recovered from bodies of deceased men in the territory of the Sakha (Yakutia) Republic. The material was collected in the summer (June, July, and August) and winter (December, January, and February) seasons of the year with the support from the State Budget Institution of the Bureau of Forensic Medical Examination of the Sakha (Yakutia) Republic. Death caused by low natural temperature occurred most often at ambient air temperatures ranging from  $-34^{\circ}\text{C}$  to  $-40^{\circ}\text{C}$ , less often at  $-31^{\circ}\text{C}$  to  $-33^{\circ}\text{C}$ . As one of the most frequent factors contributing to the onset of death from hypothermia is alcohol intoxication, for comparative characteristics of the morphology of lymphoid tissue, we also investigated the group of persons who died from general hypothermia with underlying alcohol intoxication.

Thus, all studied deceased bodies were divided into 3 groups: the first – persons who died in the summer from fatal mechanical injury, had no respiratory system pathology (control group); the second – persons who died from general bodily hypothermia (GBH) in the winter season; the third – persons who died in the winter season from alcohol intoxication (AI), who had no respiratory system pathology during their lifetime.

The material was fixed in a 10% neutral formalin solution, embedded in "Histomix" paraffin. Paraffin blocks were cut on a Leica HL 1210 microtome at slice thickness of 0.3-0.5  $\mu\text{m}$ . Sections for histological review were stained with hematoxylin and eosin. Cytoarchitectonics of lymphoid structures were studied using a Leica DMD light microscope under oil immersion at 90x magnification, using a 25-node ocular morphometric grid of Stefanov S.B. [14]. Counting of cells (per unit area  $S = 0.016 \text{ mm}^2$ ) was performed in surface epithelium, in laryngeal mucous coat and in the submucosal layer. During the analysis and histological preparations we accounted for small, medium, large lymphocytes, immature and mature plasma cells, macrophages, mast cells, eosinophils, neutrophils, fibroblasts,

cells in a state of mitosis, and destructively altered cells. The data obtained were recorded as tables. Statistical processing of the obtained data was carried out according to the method of variation statistics with the definition of arithmetic mean ( $\bar{X}$ ) and its margin of error ( $S_{\bar{X}}$ ). The significance of differences with the p-95% reliability ( $p < 0.05$ ) was estimated by method of confidence intervals between Student's t-distribution indicators [2, 8]. All mathematical calculations were carried using Microsoft Office Excel 2007 table editor.

Immunophenotyping of T- and B-lymphocytes and macrophages (CD3 +, CD20 +, CD68 +) was performed using the PolyVue Mous/Rabbit HRP Kit (manufacturer Diagnostic BioSystems, USA) imaging system according to the instructions of the manufacturer. Antigen unmasking was performed for 2 minutes in citrate buffer (pH 6.0). Primary antibodies (CD20 +, CD3 +, CD68 +) were incubated at  $37^{\circ}\text{C}$  for one hour. The result of the reaction was visualized with diaminobenzidine [4, 9, 10]. Microscopy of immunohistochemical preparations was carried out in transmitted light using a Leica DMD microscope under oil immersion with 90x microscope magnification. Photographing of microsections was carried out using a Leica digital microscope.

#### Research Results & Discussion.

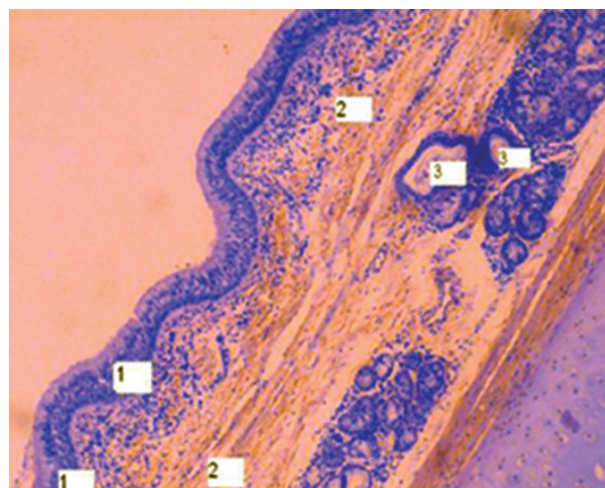
The mucosa-associated lymphoid structures of the larynx are represented by both diffuse lymphoid tissue and an accumulation of lymphoid cells. Diffuse lymphoid tissue is found in the epithelium, in the lamina propria of the mucous membrane and in the submucosal layer of all parts of the organ, and lymphoid accumulations are located in the region of the vestibule, the ventricles and the anterior wall of the subglott region. This article presents the results of a morphological study of cells of the diffuse lymphoid tissue of the mucous membrane of the ventricles of the larynx.

Our research has shown that the effect of low natural temperature on the human body leads to significant morphofunctional changes in the mucous membrane

of the larynx, both in persons who have died from a general hypothermia of the organism, and in persons who have died from general hypothermia of the organism against the background of alcohol intoxication. Thus, a stratified squamous epithelium swells, a large amount of mucus is deposited in the epithelial cells, edema is observed in the mucosa itself, the glands and excretory ducts dilate, and the accumulation of mucus in the lumens (Fig. 1).

In the epithelium of the ventricles of the larynx with general hypothermia, the number of reticular cells decreases by 1.2% compared to the control group, the number of large lymphocytes decreases by 36.6% compared to the control group and by 13.1% compared with the group who died from alcohol intoxication. The number of medium lymphocytes decreases by 0.3%, small lymphocytes – 1.6% less compared with the control group and 4.5% less compared with alcohol intoxication, plasma cells – 1.2% more. Significantly increase in the number of cells in a state of destruction – 22.2% more compared with the control group and 20.3% more compared with alcohol intoxication, macrophages – 14.3% more compared with the control group and 1.7% more compared to with alcohol intoxication.

In the lamina propria of the laryngeal mucosa, the number of reticular cells decreases by 2.1% compared with the control and 2% compared with alcohol intoxication; the number of large lymphocytes decreases by 13.7% compared to the



**Fig.1.** The mucous membrane of the vestibule of the larynx in conditions of exposure to low natural temperatures in the winter season. The epithelial layer is swollen, thickened, in the goblet cells the deposit of mucoid secretion (1), in the lamina propria of the mucous membrane edema (2), the excretory ducts of the glands are enlarged, and in the lumens there is an accumulation of mucoid secretion (3). Stained with hematoxylin and eosin. Zoom of approximately 7 by 25

control and 10.1% by compared with alcohol intoxication, medium lymphocytes – by 5.3% compared with the control and 3.2% compared with alcohol intoxication, small lymphocytes – by 1.5% compared with the control. In the group of persons who died from general hypothermia of the organism, the number of plasma cells in the mucosa itself was reduced by 3.2% compared with the control group and 2.4% compared with alcohol intoxication. The number of destructively altered cells due to general hypothermia increased by 11.1%, macrophages by 5.4% compared with the control group, and compared with alcohol intoxication of cells in a state of destruction increased by 14.4%.

In the submucosal layer of the ventricles of the larynx, the number of large lymphocytes decreases by 4.9% compared with control and by 11.2% compared with alcohol intoxication. Medium, small lymphocytes and plasma cells in the submucosal layer of the larynx did not occur in general hypothermia of the organism, at the same time we found the presence of single eosinophils not found in the control group and the group of alcohol intoxication. The number of macrophages compared with the control and alcohol intoxication increases – by 6.2% and 3.5%, respectively.

The results of the immunohistochemistry study of the local immune system of the mucous membrane of the laryngeal ventricles in individuals who died from hypothermia compared with those who died in the summer period showed a decrease in T-cell (CD3 +) by 24%, B-cell link (CD20 +) – by 17% and activation macrophageal histiocytic cell population (CD68 +) - by 11% (Fig. 2). Our research allows us to confirm the data of many authors [1, 7, 11, 12], who claim that when the body is exposed to low natural temperatures, cellular and humoral immunity is suppressed.

### Conclusions

1. Peripheral immune structures (MALT - mucosa-associated lymphoid tissue) are highly sensitive to the effects of low natural temperatures, which manifest itself in the form of pathological changes of diffuse lymphoid tissue in the mucous membrane of the larynx.

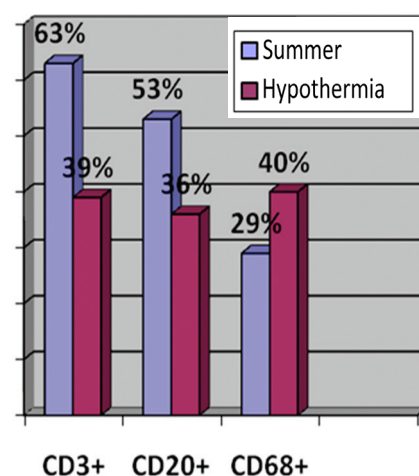
2. Changes in the mucosa-associated diffuse lymphoid tissue in the mucous membrane of the larynx when exposed to low natural temperatures are characterized by a significant decrease in lymphopoietic processes, which results in a decrease in the percentage of lymphoblastic cells and cells in a state of mitosis.

3. Exposure to low natural temperatures in the Sakha (Yakutia) Republic causes depletion of mucous-associated diffuse lymphoid tissue of the laryngeal mucosa, which is expressed by a decrease in the number of lymphoid cells, in particular T-lymphocytes, B-lymphocytes, plasma cells, and also a significant increase in the number of destructive altered cells, and as a result, macrophages.

4. To improve the quality of pathological diagnosis of death from general hypothermia when exposed to low natural temperatures, it is recommended to use the study of the cellular composition of diffuse lymphoid tissue of the mucous membrane of the larynx.

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**Fig.2.** The immune status of diffuse lymphoid tissue of the ventricles of the larynx in individuals who died from general hypothermia compared with the control group (CD3 + – T-cell antigen; CD20 + – B-cell antigen; CD68 + is a macrophage marker (monocytes and histiocytes)

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## METHODS OF DIAGNOSIS AND TREATMENT

A. V. Antonov, V. E. Volovik, G. A. Palshin

# THE ROLE AND THE PLACE OF ARTHROSCOPY OF THE HIP JOINT IN TREATMENT OF ASEPTIC NECROSIS OF THE FEMORAL HEAD

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#### ABSTRACT

Aseptic necrosis of the femoral head (ANFH) is one of current problems in orthopedics today. The arthroscopy of a hip joint in ANFH is a modern way of minimal-invasive surgery. We use the following staged means of arthroscopy: capsulotomy and synovectomy, debridement and sanation of a joint, revision of degenerative and dystrophic changes, resection of the affected cartilage, microfracturing, removal of free microscopic and macroscopic fragments of cartilage. The quality of life in operated patients before and after was estimated on Harris Hip Score (HHS). Arthroscopy of the hip joint has shown the positive clinical results and indeed improves quality of life in patients. It is necessary to revise more deeply all possibilities of arthroscopic surgery of the hip joint, to estimate all results, to improve treatment methods and to achieve long remission of a disease.

On the basis of the orthopedic department of the KGBUZ Regional Clinical Hospital No. 2 in Khabarovsk, an analysis of the frequency of occurrence of aseptic necrosis of the femoral head, its various diagnostic methods, conservative and operative treatment, and the pathological picture of the disease among the adult population in various age categories was made. The obtained positive results of treatment indicate the need for further study of the problem in order to achieve a long lasting remission, and possibly a complete recovery of the patient.

**Keywords:** arthroscopy, aseptic necrosis of the femoral head.

**Introduction.** Aseptic necrosis of the femoral head (ANFH) is wide spread multifactorial poliethiologic disease affecting primarily men of working age, the initial link in the pathogenesis of which is not exactly understood. ANFH diagnosis presents considerable difficulties, due to the late-stage patients, late medical care, and the absence of clear diagnostic symptoms. Edema of the bone marrow in the initial stage of the pathological process can be detected only on MRI investigation. Traditional conservative treatment has not enough effectiveness and provides short-term improvement only in the early stages of the process due to the use of drugs with low or unproven effectiveness, and anyhow results the complete replacement of the joint only for a short period of time. Surgical methods mostly are traumatic and require long-term rehabilitation, while not providing for long-term remission, and hip replacement is associated with high risks of components' instability.

Nowadays, one of the little-known methods of surgical treatment in ANFH patients is arthroscopy of the hip joint [8, 9].

#### Materials and methods of research.

On the basis of Territorial state educational Health facility "Regional clinical hospital №2" in Khabarovsk we've analyzed the frequency of aseptic necrosis of the femoral head, different methods of its diagnostics, conservative and surgical treatment, as well as the pathological picture of the disease among the adult population of different age. From 2015 to 2017, 97 patients diagnosed with aseptic necrosis of the femoral head of the 2nd-4th degree (according to ARCO) were treated in the hospital, which is 25% of all degenerative diseases of the hip joint. 53% of the cases were middle-aged women (45-59 years).

The **purpose** of the study is to analyze the frequency of ANFH occurrence.

**Results and discussion.** Detection of the disease ANFH at an early stage in most cases is extremely difficult and formed 9 percent of cases, post-traumatic ANFH - 13% of patients and 4% had congenital abnormalities of the hip joint [3].

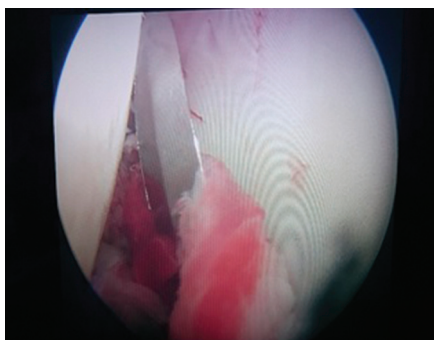
Complaints of patients after hospitalization are usually non-specific, which is probably is one of the reason for incor-

rect interpretation at the ambulant stage of examination: permanent pain syndrome (93%), increasing under weight load (92), accompanied by a violation of limb function (98) and requiring the use of additional means of support in movement (64%).

Despite the development of modern highly informative radiographic methods of diagnosis, the main standard of examination is radiography of the affected joint, and an additional method of investigation only in 4% of cases is magnetic resonance imaging.

Late-stage pathological process, the severity of clinical symptoms lead to the surgical treatment, which was performed in 65% patients. Mostly total cementless hip replacement (Zimmer, DePuy). In 1% of cases, due to instability of the acetabular component, augments were used during the press-fit. Instability of the endoprosthesis components in late follow-up occurred in 3% of cases, all around implants with a cement type of fixation.

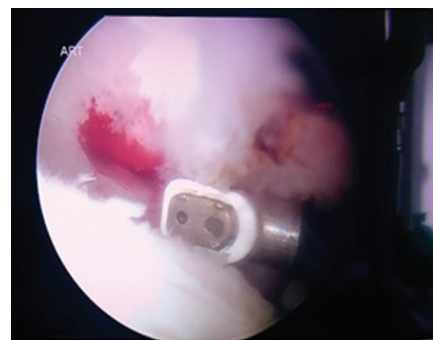
Intraoperative autopsy material was taken for histological examination in 50 patients, both who undergone total hip replacement and core decompression. In



**Fig.1.** Anterolateral and posterolateral capsulotomy with an arthroscopic BEAVER knife



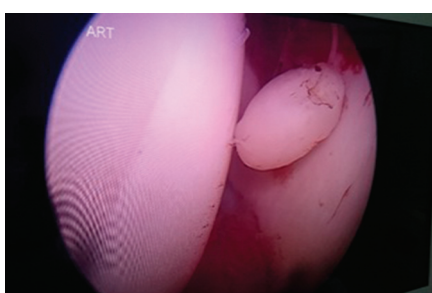
**Fig.2.** Revision of the joint by a Shaver (arthroscopic picture of the hip joint in ANFH)



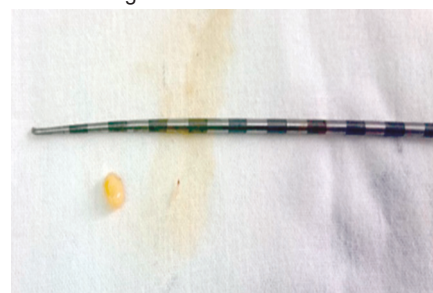
**Fig.3.** Revision of the joint by VAPOR-electrode, removal of degenerative changes of the cartilage elements



**Fig.4.** Diagnostics of degenerative changes in the cartilaginous tissue of the femoral head for subsequent microfracturing



**Fig.5.** Visualization of free osteochondral fragments in the hip joint



**Fig.6.** Chondroid corps from the hip joint after removal

most cases, specimen had signs of fatty degeneration of the bone marrow in a ratio of 5: 1, with the presence of fibrous tissue, signs of resorption, necrobiosis, lymphoid-plasmocytic and histocytic infiltration of the stroma, and in some cases, signs of an inflammatory reaction.

Arthroscopic revision of the hip joint included the following stages:

1) anterolateral and posterolateral capsulotomy with an arthroscopic BEAVER knife (Fig.1),

2) revision of the joint by a Shaver (Fig.2),

3) revision of the joint by VAPOR-electrode, removal of degenerative changes of the cartilage elements (Fig.3),

4) diagnostics of degenerative changes in the cartilaginous tissue of the femoral head for subsequent microfracturing (Fig.4),

5) visualization of free osteochondral fragments in the hip joint (Fig.5),

6) removal of the chondroid corps from the hip joint (Fig.6).

Results were fixed and evaluated on the Harris hip scoring system (HHS). Before surgery HHS ranged from 24 to 70. According to preliminary results, we have got 60% positive results, 20% of them correspond to the excellent result of treatment, 20% – good and 20% – satisfactory, 40% of the results were assessed as unsatisfactory because of the persisting pain syndrome with up to 68 HHS.

**Conclusion.** Aseptic necrosis of the femoral head is one of the urgent prob-

lems in modern orthopedics. Arthroscopic diagnostics of the pathological process with subsequent revision of the hip joint, capsulotomy and synovectomy gives a decompressing effect, reduce the tension of the joint capsule, makes it possible to remove free osteochondral fragments and areas of cartilage detachment with microfracturing if necessary, which allows to preserve the cartilage of the femoral head, thereby ensuring its stable function for an indefinite period of time. Positive experienced results of treatment dictate the need for further study of the problem, observation of patients and analysis of long-term results of treatment in order to achieve the longest possible remission, and in some cases, complete recovery of the patient.

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## BASIC PRINCIPLES OF SURGICAL TREATMENT OF ARTIFICIAL PYOINFLAMMATORY DISEASES OF SOFT TISSUES

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### ABSTRACT

**Aim.** To identify the peculiarities of surgical treatment of APIDST.

**Material and methods.** The analysis of treatment of 302 men with APIDST in the department of purulent surgery of the 301 Military Clinical Hospital of Khabarovsk from 1987 to 2013 was carried out.

**Results.** Surgical emergency procedures were performed in 40 (13.2%) patients with APIDST before admission to the hospital and in 262 (86.8%) patients with APIDST immediately after admission to the hospital. Necrectomy was performed in 6 (2.0%) patients with APIDST before admission to the hospital and in 118 (39.1%) patients with APIDST immediately after admission at the hospital. The signs of anaerobic infection were found during the surgical procedures in 260 (86.1%) patients. During hospitalization 2 or more surgical procedures were required in 188 (62.3%) patients with APIDST due to the progression of the disease.

**Conclusions.** In case of substantiated suspicion of APIDST surgical intervention should be based on the main principles of surgical treatment of anaerobic infections regardless of the duration of the disease. It is recommended to start the procedures with a small diagnostic incision through the site of introduction of the initiating substrate with a mandatory revision of the subfascial space and performing radical necrectomy.

**Keywords:** artificial pyoinflammatory diseases of soft tissues, treatment.

#### List of reductions:

APIDST – artificial pyoinflammatory disease of soft tissues.

**Introduction.** The choice of treatment strategy of APIDST is a very difficult problem due to insufficient knowledge of this pathology. It was established, that after deliberate introduction of non-sterile biological fluids into the soft tissues anaerobic infection develops in the majority of cases [3,16]. Various chemicals, introduced into soft tissues, cause «chemical» necrosis, progressive ischemia, creating conditions for the development of anaerobic infection [9,15]. It is well known that anaerobic infection of soft tissues holds a special place among surgical infections due to the high morbidity and mortality [4,5]. Currently, some experts are sure that the treatment strategy of APIDST, caused by non-sterile biological fluids, does not seriously differ from the conventional

approach to the treatment of surgical soft tissue infections and does not have any specific features [13]. Other authors stick to the opinion that the treatment of APIDST has some specific features, particularly in patients after introduction of a chemical initiating substrate into the soft tissues of the body [9,15,18].

The aim of this work is to identify the peculiarities of the surgical treatment of APIDST.

**Material and methods of the research.** The analysis of treatment of 302 men with APIDST who accounted for 6,1% of all patients with different forms of surgical infections of soft tissues and had been hospitalized to the department of purulent surgery of the 301 Military clinical hospital of Khabarovsk from 1987 to 2013, was carried out. The

most commonly used disease initiating substrates were oral fluid (36.1%), dental plaque (15.6%) and liquid hydrocarbons (6.3%).

**Results and discussion.** Of 302 patients with APIDST, surgical emergency procedures were performed before admission to the hospital in 40 (13.2%) patients, and immediately after admission to the hospital - in 262 (86.8%) patients (Table 1).

As is seen from the above table, radical treatment of the surgical infection focus including not only an adequate incision but also necrectomy was performed in 6 (2.0%) patients with APIDST before admission to the hospital and in 118 (39.1%) patients with APIDST immediately after admission to the hospital (Table 1).



In the course of treatment, some patients required repeated operations due to the progression of the inflammatory process (Table 2).

As is seen from the above table, 188 (62.3%) patients with APIDST required 2 or more surgical procedures (Table 2).

The distribution of patients with APIDST depending on the area of the inflammatory process is presented in Table 3. The area of the inflammatory process indirectly indicates the average length of the incision.

The area of the inflammatory process was limited and accounted for less than 500 cm<sup>2</sup> in 184 (60.9%) patients and more than 500 cm<sup>2</sup> - in 118 (39,1%) patients with APIDST (Table 3).

The signs of anaerobic infection were found during the surgical procedures in 260 (86.1%) patients.

The peculiarities of surgical procedures in patients with APIDST were as follows. Surgical intervention was started from making a small (diagnostic) incision through the point of introduction of the initiating substrate under local anesthesia, which together with the other diagnostic procedures allowed to reliably confirm APIDST.

In our opinion, an incision at some distance from the point of introduction of the initiating substrate is the most common mistake.

The information obtained during a small diagnostic incision was used to select the type of anesthesia in the main stage of the surgical procedure as well as to plan the direction of the operative access and to determine the borders of necrectomy. Besides, the material for emergency bacterioscopy and tissue biopsy was taken from the wound for microbiological investigation.

In spite of the absence of visible changes in the subcutaneous tissue and fascia in some patients, revision of the subfascial and intermuscular space was obligatorily performed.

During the main stage of surgery, the pathomorphological form, the severity of the inflammatory process as well as the particular features of the soft tissues destructive changes were clarified. The decision on whether additional incisions should be performed was taken.

The maximum possible necrectomy, debridement of the wound and its drainage were carried out if necessary.

We avoided to perform additional incisions, particularly located close to each other. We think, that one or two adequate incisions are sufficient for the revision of the surgical infection focus.

It should be noted that, in our opinion, the practice of making short incisions

**Table 1**  
**Surgical emergency procedures, performed in patients with APIDST before and after admission to the hospital**

Surgical procedures	Before admission		After admission	
	n	%	n	%
The number of patients to have been operated on	40	13.2	262	86.8
Cases of radical necrectomy performed	6	2.0	118	39.1

**Table 2**  
**Number of surgical procedures in patients with APIDST**

The number of performed surgical procedures per a patient	APIDST (n=302)	
	n	%
1 surgical procedure	114	37.7
2 surgical procedures	95	31.5
3-5 surgical procedures	72	23.8
6-9 surgical procedures	15	5
10 or more surgical procedures	6	2

located close to each other is wrong, because such incisions do not allow to perform an adequate revision and necrectomy, creating conditions for the progress of the purulent and destructive process. In addition, several small incisions often lead to the necrosis of the tissues between them.

During necrectomy, the wound was carefully cleaned with antiseptic solutions. Hemostasis was performed using diathermocoagulation, as the ligation of vessels often promotes the development of ischemia and increases the contamination of viable tissues with anaerobic microorganisms.

After completing the surgical procedures, the resulting wound was loosely packed with napkins soaked with anti-anaerobic activity ointments.

The wound tamponade was performed in such a way that there were no empty pockets and cavities left. The need for repeated necrectomy and application of bandages was determined based on the monitoring of the patients' condition and the development of the wound process. There was no mortality in this group of patients.

Currently, the active treatment strategy of anaerobic soft tissue infection is accepted. It includes the early surgical procedures, the removal of all necrotic tissues, active drainage and aeration of the wound [5,13,7]. Such strategy allows to reduce mortality from 40-67% [2, 4, 6] to 13-29.7% [8,7,17].

Considering that anaerobic microorganisms are involved in the majority of APIDST cases, the surgical procedures must be performed in all patients according with fundamental principles of surgical treatment of anaerobic infection of soft tissues.

We deem it appropriate to resort

**Table 3**  
**The area of the inflammatory process in patients with APIDST**

The area of the inflammatory process in patients	APIDST (n=302)	
	n	%
Less than 500 cm <sup>2</sup> (3% of the area of the person's skin)	184	60.9
From 500 to 1000 cm <sup>2</sup> (3-6% of the area of the person's skin)	88	29.1
From 1000 to 1500 cm <sup>2</sup> (6-9% of the area of the person's skin)	21	7
More than 1500 cm <sup>2</sup> (>9% of the area of the person's skin)	9	3

to surgical intervention in all cases irrespective of the duration of the disease if there is a substantiated suspicion of APIDST.

We share the opinion of M. J. DiNubile [8], that in case of a suspected anaerobic infection of soft tissues, "an early or a too extensive surgical procedure would be a much safer option".

Considering that it is not possible to diagnose anaerobic infection with a high degree of probability before the surgical procedure, the intraoperative assessment of tissues is needed [1,6,8], which according to our observations allows to establish the anaerobic nature of the disease in 86.1% of patients. The above mentioned changes of tissues include such well-known signs of anaerobic infection as the stinking smell of gray-green or brown exudate, a specific type of diseased tissues of gray, gray-green or black color, liquid pus, often diffusely saturating the inflamed tissues, the presence of gas and the presence of wound anaerobic microorganisms in the smears [1,4,6].

The early diagnosis of anaerobic infection of soft tissues is extremely important; therefore, we share the opinion of some authors who insist that the diagnosis of anaerobic infection must not be questioned when we can find at least one of the above-mentioned signs. In such a case, the isolation of the causative agent to prove the participation of anaerobes in the infectious process is not of paramount importance [1].

As far as the chemical substances are concerned, many authors agree

that the first step in the treatment of APIDST caused by chemicals, for example, by liquid hydrocarbons, is the urgent hospitalization of patients to the hospital for observation and prevention of systemic complications [9,15,18].

At the same time, the analysis of modern publications on APIDST reveals the lack of a common approach. A number of researchers support the conservative approach consisting in the forming of the elevated position and immobilization of the affected limb, dynamic observation and symptomatic therapy without denying surgery in case of the negative dynamics of disease and the development of local complications [15,18].

At the same time, other authors point out the need for emergency surgery, regardless of the patient's condition, local status and the time elapsed since the introduction of the chemical. Surgery in these cases usually is based on the extensive access, adequate necrectomy, possible fasciotomy and wound drainage. Subsequently, in some cases repeated surgical treatment of the wound is performed [11, 12].

In the review of Kennedy J. R. et al. (2010) [10], which analyzes the treatment of APIDST caused by chemicals, the authors insist on emergency surgical treatment of the wound in order to prevent tissue necrosis by removing toxic exudate from the wound, and to prevent the compartment syndrome and to stop the resorption of chemicals.

Our experience of the treatment of patients with APIDST caused by chemicals confirms the feasibility of active surgical treatment of them, based on principles of treatment of anaerobic infection.

### Conclusions

1. Diagnosis of anaerobic infection in cases of APIDST should be based primarily on the detection in the course of a small diagnostic incision of signs indicating the anaerobic nature of the disease.

2. Surgical intervention in case of the reasonable suspicion of APIDST must be performed taking into account the main principles of treatment of anaerobic infections, regardless of the stage of the disease.

3. Surgical intervention should begin with a small diagnostic incision through the site of introduction of the initiating substrate with a mandatory revision of the subfascial space and performing a radical necrectomy.

4. In surgical treatment of patients with APIDST induced by chemicals one should resort to active surgical treatment with consideration for the basic principles

of treatment of anaerobic infection.

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## POSTLINGUAL DEAFNESS IN EVENO-BYTANTAYSKY NATIONAL DISTRICT OF THE SAKHA REPUBLIC (YAKUTIA): AUDIOLOGICAL AND CLINICAL-GENEALOGICAL ANALYSIS

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### ABSTRACT

In this paper we present for the first time the results of the audiological and clinical-genealogical research of the population of settlements Batagai-Alyta and Kustur of the Eveno-Bytantaisky National District (ulus) of the Sakha Republic (Yakutia) for studying the postlingual form of deafness of unknown etiology, which we for the first time have identified earlier in 3 Evens. As a result of an audiological examination of 72 people, 10 patients from 6 nuclear families who met the criteria of postlingual form of hearing loss were found. The segregation analysis carried out in these families confirmed the autosomal recessive type of inheritance of this form of postlingual hearing loss. The distant relationship of the examined patients with postlingual hearing loss living in two villages of the Eveno-Bytantaisky National District of the Sakha Republic can indicate to the role of the founder effect in the local prevalence of this pathology. The results of present study and obtained expedition material will be the basis for further research of the molecular genetic etiology of this form of deafness and the discovering of mechanisms of its accumulation in this region of Yakutia.

**Keywords:** postlingual deafness, audiological analysis, clinical-genealogical analysis, segregation analysis, Eveno-Bytantaisky National District, Sakha Republic (Yakutia).

**Introduction.** Mutations of the *GJB2* gene are the main reasons of congenital and prelingual nonsyndromic hearing loss (HL) in many countries [5, 10]. Currently the territory of Eastern Siberia (the Sakha (Yakutia) Republic) is characterized by the spectrum and frequency of mutations of the *GJB2* (Cx26) gene on the large cohort of patients (n=393) with congenital hearing impairments and individuals with normal hearing (n=187) from Yakut and Russian populations [1, 9]. Recently it was shown that the pathogenic contribution of biallelic *GJB2* gene mutation to the etiology of HL in Yakutia was equal to 49%; and this rate was the largest in comparison with the earlier studied regions of Asia (10213 probands from 23 countries) [4]. In the spectrum of identified *GJB2* mutations, three mutations: c.-23+1G>A, c.35delG and c.109G>A were the most common. These mutations account for 98% out of all pathogenic *GJB2* alleles. The major *GJB2* mutations specific for the main ethnic populations of Sakha (Yakutia) Republic were identified:

for the Yakuts - c.-23+1G>A and for the Russians - c.35delG. Nevertheless, the biallelic *GJB2* mutations were not detected in 51% of examined deaf patients (*GJB2*-negative patients), and the reason of their HL remained unknown. Considering the genetic diversity of known hereditary forms of deafness, there is a high probability that HL of some patients may be due to the mutations in other genes since about 100 genes are known in association with non-syndromic hearing impairments (Hereditary Hearing loss Homepage - <http://hereditaryhearingloss.org>).

Our detailed clinical-genealogical analysis of the sample of *GJB2*-negative patients from different districts of the Republic of Sakha (Yakutia) revealed 3 Evens with late onset HL from the village Batagai-Alyta (Eveno-Bytantaisky National District): 2 sibs (proband A and sibs A) whose HL became noticeable at 7 years in proband A and at 4 years in sibs A, and also one patient (proband B) with the same onset of HL (at 4 yrs).

All collected data (medical history, the results of molecular-genetic and audio-

logical analysis) for these 3 patients from the Eveno-Bytantaisky National District of the Sakha Republic allowed us to suggest the hereditary cause of this postlingual form of deafness.

The **objective** of this study is to conduct audiological and clinical-genealogical analysis of the families with postlingual form of deafness of unknown etiology from Eveno-Bytantaisky National District for the further confirmation of hereditary nature of this disease and clarification of its inheritance type.

**Materials and methods of the research.** During the field work in the Eveno-Bytantaisky National District of the Sakha (Yakutia) Republic (April, 2018) the staff of the Yakut Science Center of Complex Medical Problems (Yakutsk) examined 106 inhabitants of the villages Batagai-Alyta and Kustur. Among them, 72 individuals were selected for the study of the etiology of the postlingual form of deafness - 65 from Batagai-Alyta, 4 from Kustur, and also 3 previously examined *GJB2*-negative patients (proband A, sibs A, proband B) from Batagai-Alyta were taken for further examination. Among

\* - These authors contributed equally to this work



them, males accounted for 34.7% (n=25), females - 65.2% (n=47). The average age was  $44 \pm 17.21$  years. Ethnic composition of the sample: Evens - 48 (66.6%), Yakuts - 22 (30.5%), one Evenk (1.4%), and one individual of mixed ethnicity (Even/Yakut) (1.4%).

### Audiological examination

Complaints about the condition of hearing such as the presence of a discharge from the ear, noise in the ears, dizziness were clarified through an interview with patients. Medical and life histories including past illnesses, injuries and/or surgeries, contacts with industrial noise, and information about allergic reactions was ascertained for all examined subjects. The otologic examination was carried out by unified algorithms on the KaWe Combilight otoscope. A full audiological survey was conducted with the use of a tympanometer and an audiometer "AA222" ("Interacoustics", Denmark). Hearing thresholds were measured by air conduction at frequencies of 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 kHz and bone conduction at frequencies of 0.25, 0.5, 1.0, 4.0 kHz in 5.0 dB increments. Severity of HL was defined by hearing thresholds of better hearing ear in the voice frequency range (VFR) in accordance with international classification under which I degree is equal to 26-40 dB in VFR, II - 41-55, III - 56-70, IV - 71-90, deafness > 90 dB.

### Clinical-genealogical analysis

We had developed an individual card, which included information about last name, first name, middle name of the

participant and his parents and grandparents; age; ethnicity (up to the third generation); place of birth and residence as well as the profession was filled out for each participant. The information about otorhinolaryngologic diagnosis, potential cause of HL, onset of HL, presence or absence of relatives with HL, and concomitant diseases was also included in the individual patient's card. The pedigrees compiled on the basis of all obtained data were subjected to subsequent clinical-genealogical analysis.

To confirm the heritability of postlingual form of HL and ascertain the type of its inheritance we conducted a segregation analysis in six nuclear families selected through the proband (Table 1). All parents in these families were healthy that suggests a recessive type of the inheritance of this trait.

The Weinberg formula for a single choice was used for calculation of the segregation frequency (SF) of the trait in families [11]:

$$SF = (r - n) / (s - n), \quad (1)$$

where  $r$  - the number of affected subjects in all siblings,  $n$  - the total number of probands,  $s$  - the total number of descendants in the sample.

The standard deviation was calculated as:

$$\sigma = \sqrt{SF(1 - SF)/(s - n)} \quad (2)$$

To test the hypothesis about the type of inheritance, a confidence interval (CI) was calculated as:

$$CI = SF \pm 1.96 * \sigma \quad (3)$$

The hypothesis is accepted if the ex-

**Table 1**  
Data for segregation analysis in families of patients with signs of postlingual form of deafness/hearing loss

Sibship's size (s)	Nuclear families/probands (a)	Affected siblings (r)		
		1	2	3
2	2	2	-	-
3	2	1	1	-
7	1	-	-	1
9	1	-	1	-
Total	6	3	4	3

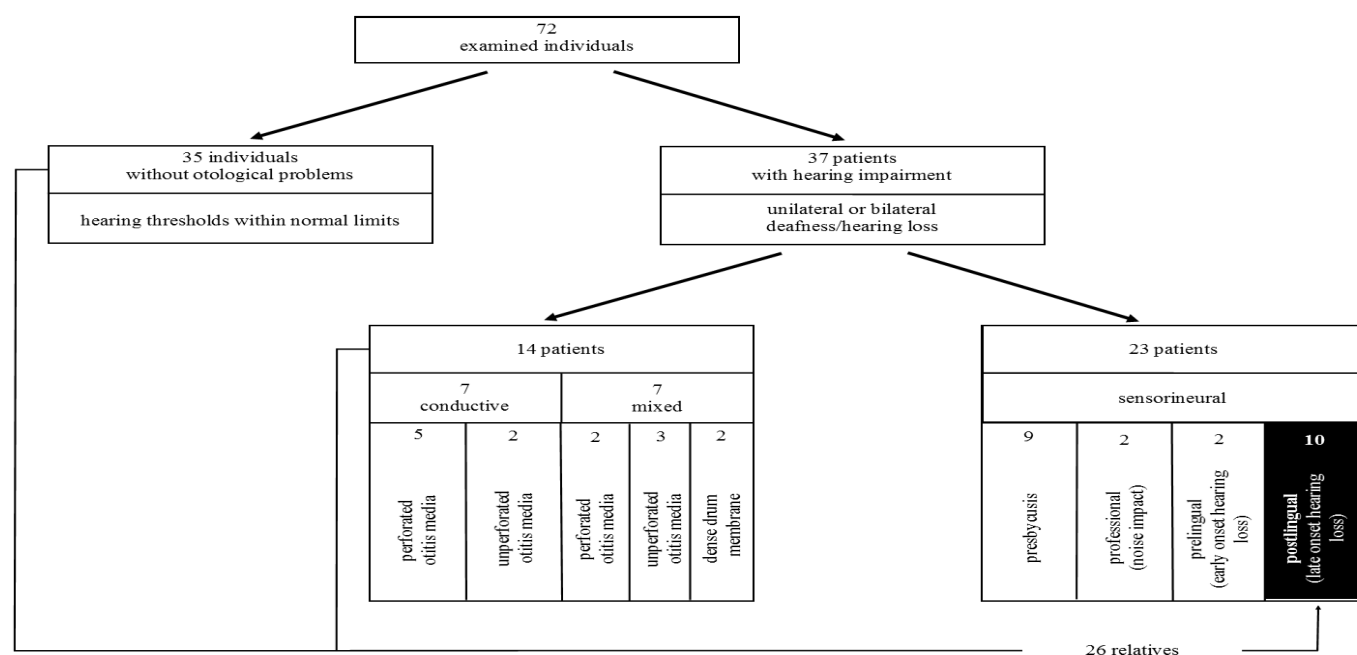
pected value of the segregation frequency (0.25 for recessive inheritance) falls into this interval.

All examinations provided in this study have been conducted after written consent of all participants or their parents. This study was approved by the local Biomedical Ethics Committee of Federal State Budgetary Scientific Institution "Yakut Science Centre of Complex Medical Problems", Yakutsk, Russia (Protocol No. 16, April 16, 2009).

### Results and discussion

#### Audiological analysis

Among 72 examined individuals 35 subjects did not complain about HL and audiological examination has not revealed any objective otologic problems (normal hearing thresholds were detected). Unilateral or bilateral HL was observed in 37 individuals (the possible causes of HL are shown in Fig. 1). Among them, the pathology of the sound-conducting system and unilateral or bilateral



**Fig.1.** Schematic representation of the results of audiological analysis.

Note: 26 individuals from all examined subjects are relatives (of different degree of kinship) of proband A with postlingual form of deafness.

conductive or mixed HL were objectively detected in 14 patients. 23 patients had unilateral or bilateral sensorineural HL in the absence of a visual otological problem. Among these 23 patients with sensorineural HL, 12 patients had no opinion about causes of their HL, 2 patients supposed otitis media in childhood, 2 patients - possibly toxic exposure to antibiotics, 2 patients - head injury in childhood, 1 patient - hereditary HL, 1 patient - colds, 1 patient - age, 1 patient - industrial noise exposure. Among 23 patients

with sensorineural HL, 9 patients showed signs of presbycusis, 2 patients showed signs of noise exposure, 2 patients had a prelingual (before 1 year) HL, and 10 had signs of postlingual HL that had become noticeable at the age of 3 - 48 years. In total, as a result of the audiological analysis 10 patients (5 males and 5 females from 18 to 65 years old, whose average age at the time of the study was  $43.3 \pm 13.7$  years), showed the signs of postlingual form of HL which firstly detected by us in 3 patients (proband A,

sibs A, proband B) (Table 2).

These patients were predominantly Evens (Evens - 8, Yakuts - 2) that probably indicates the ethnic specificity of investigated form of HL.

#### Clinical-genealogical analysis

Based on the initial analysis of personal data, we found that 72 examined individuals belonged to 24 families with 718 family members in total. Among them, 10 patients with signs of postlingual form of HL belonged to three extended pedigrees (355 relatives in total) (Fig. 2). At

Characteristics of patients with signs of postlingual form of deafness/hearing loss

Table 2

Patients	Code	Sex	GJB2 genotype	Ethnicity	Age	Diagnosis (otorhinolaryngological)	Onset of hearing loss	Subjective cause of hearing loss	Accompanying illnesses		Speech
									Otorhinolaryngological	Other	
1 Proband A	A - IV2	Female	c.[Wt];[Wt]	Even	19	Bilateral deafness	7	Not determined	Systemic hypoplasia of speech	Residual encephalopathy	Sign-dactylic language
2 Sibs A	A - IV1	Male	c.[79G>A];[Wt]	Even	20	Bilateral deafness	4	Not determined	Microtia and external auditory canal atresia	-	Sign-dactylic language
3	A - III7	Male	c.[Wt];[Wt]	Even	65	Bilateral deafness	7	Probably a trauma in childhood	Speech is absent	Glaucoma (Blindness)	Sign language
4	A - III13	Female	not investigated	Even	59	Bilateral deafness	9	Antibiotics	Dense eardrum; Chronic dystrophic rhinopharyngitis	Chronic gastritis	Sign-dactylic language
5 Proband B	A - III17	Male	not investigated	Even	57	Bilateral deafness	4	Not determined	Rinoskoliosis. Curved nasal septum	-	Sign language
6	A - III18	Male	not investigated	Even	29	Bilateral deafness	4	Colds; due to otitis media	Dense eardrum	Chronic gastritis; Neurodermatitis; Hepatitis B; Lumbar osteochondrosis	Sign-dactylic language
7	B - IV3	Male	not investigated	Yakut	38	Bilateral sensorineural hearing loss III degree	36	Not determined	Dense eardrum	Vegetative vascular dystonia according to the hypertonic type; Myopia	Intact
8	B - IV8	Female	not investigated	Yakut	42	Bilateral sensorineural hearing loss IV degree	30	Hereditary burdening	-	Chron. Pylonephritis; Cholecystitis; Chronic pancreatitis	Intact
9	C - II7	Female	not investigated	Even	54	Bilateral sensorineural hearing loss III degree	8	Not determined	-	Arterial hypertension; Diabetes II; Psoriasis; Chronic pyelonephritis; Lumbar osteochondrosis; Goiter	Intact
10	C - II9	Female	not investigated	Even	50	Bilateral sensorineural hearing loss III degree	30	Not determined	-	Mental retardation	Intact
Total		Male - 5 (50%); Female - 5 (50%)	GJB2-negative - 30%; not investigated - 70%	Even - 8 (80%); Yakut - 2 (20%)	Middle age: $43.3 \pm 13.7$	Bilateral deafness - 6 (60%) Bilateral sensorineural hearing loss - 4 (40%)	Middle age: Juvenile - $5.6 \pm 1.9$ ; Middle age: Mature - $36 \pm 6$	Not determine - 6 (60%) Other - 4 (40%)	Three people report dense eardrum - 3 (30%)	-	Absent - 6 (60%); Intact - 4 (40%)

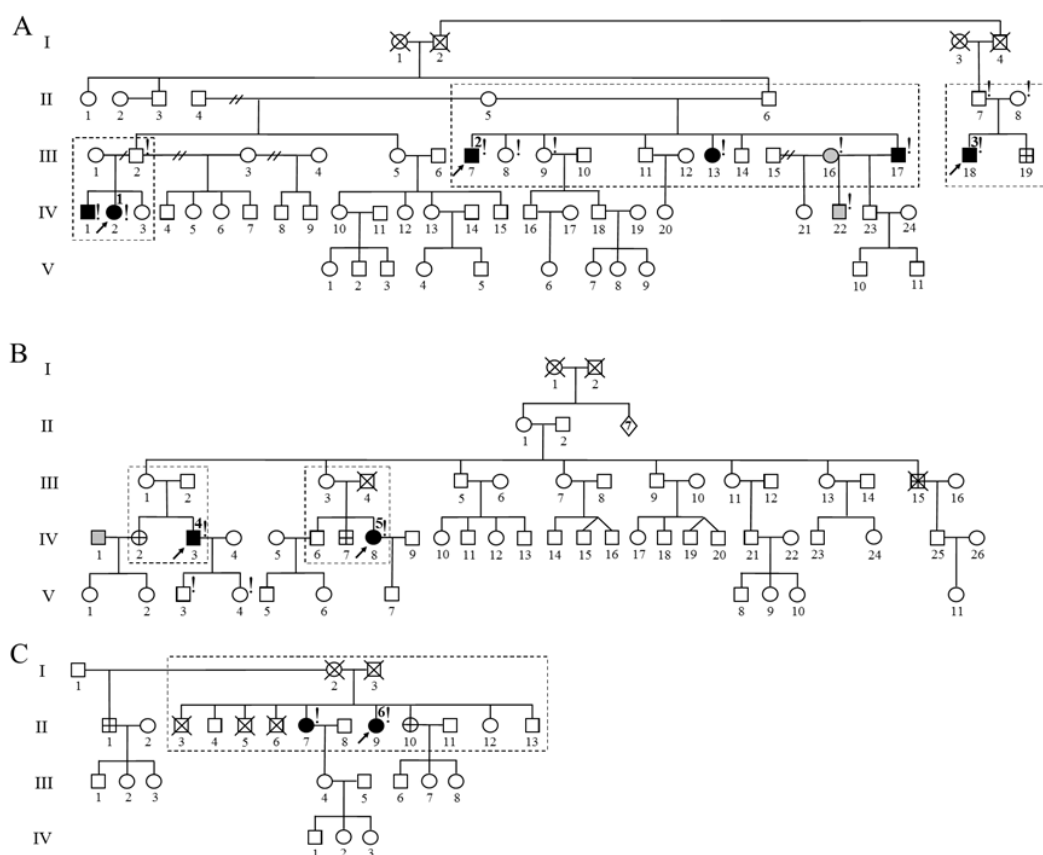
the first stage of pedigree's analysis, it was revealed that proband B (A-III17) was a paternal relative for proband A (A-IV2) and sibs A (A-IV1) (Fig. 2, A). It should be also noted that mothers (A-III1 and B-III1) of probands A-IV2 and B-IV3, respectively, are cousins (Fig. 2, A, B).

For segregation analysis we used the data on six nuclear families which included 10 patients with postlingual HL, their siblings and parents (Fig. 2). We assumed an autosomal recessive type of transmission of postlingual HL in these six nuclear families since all affected probands had hearing parents who did not complain about hearing impairment and also both deaf and hearing siblings (including cousins). To confirm or disprove the hypothesis about autosomal recessive type of inheritance of postlingual HL the segregation analysis was carried out in six siblings. Only siblings from each nuclear family were taken into account (without half-sibs and indirectly registered (on information from relatives) affected family members (Table 1). As a rule, the Weinberg proband method is used for calculation of the segregation frequency (SF) [2, 6-8, 11]. The essence of this method consists in calculating of the ratio of the total number of affected siblings to the total number of their unaffected siblings with correction for the number of probands (formula 1). The segregation frequency (SF), calculated from formula (1) with using the data from Table 1, was 0.20:

$$SF = (r - n) / (s - n) = 4/20 = 0.20$$

Subsequently, the obtained segregation frequency (0.20) was compared with the segregation frequency expected according to the recessive type of inheritance ( $SF_0 = 0.25$ ). The confidence interval calculated using formulas (2) and (3) for the obtained estimation of the segregation frequency is equal 0.026 - 0.374. Theoretically expected value of segregation frequency ( $SF_0 = 0.25$ ) falls into this interval that allows to accept the hypothesis about autosomal recessive type of inheritance of trait under study.

A common characteristic for all pa-



**Fig.2.** Pedigrees of probands with signs of postlingual form of hearing loss: A - pedigree of probands 1, 2 and 3, B - pedigree of probands 4 and 5, C - pedigree of proband 6.

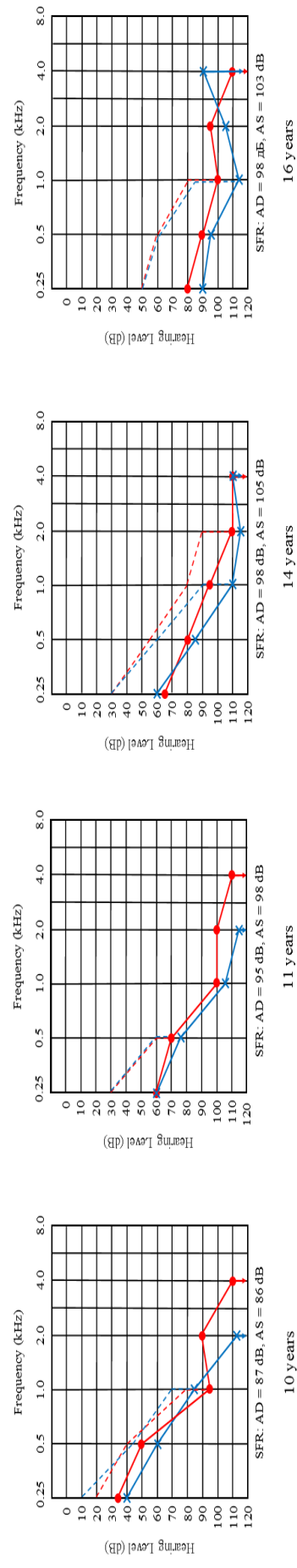
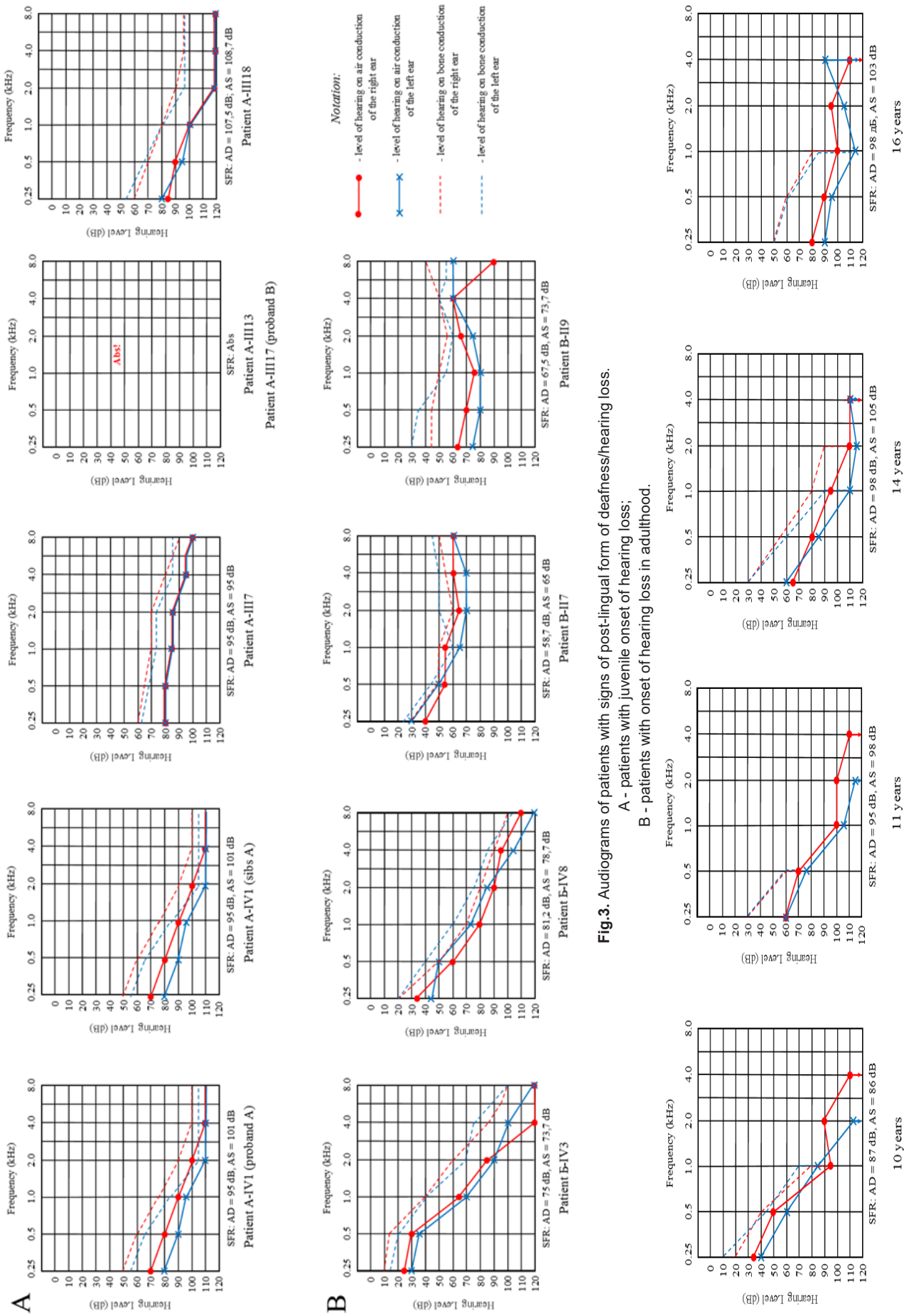
Family members with signs of hereditary postlingual form of deafness are indicated by black symbols; family members with other forms of deafness/hearing loss (congenital or conductive) – by gray symbols; family members who have signs of postlingual hearing loss (on information from close relatives) - by plus into symbols; nuclear families are highlighted by dotted lines; probands in nuclear families are denoted by arrow and number on the top.

tients is later (in comparison with congenital HL) onset of this form of HL that occurred after the end of a sensitive period of speech development (after 4-5 years and older). In this period of sensory ontogeny, verbal speech is already formed, and the thinking development of young patients approximately corresponds to the level of their hearing peers [3]. However the earlier debuts of the HL cause the sooner complete degradation of verbal speech. HL in 6 patients from our sample occurred in juvenile age (on the average  $5.6 \pm 1.9$  years), and in 4 patients with verbal speech without any special distortions - at adulthood (on the average  $36 \pm 6$  years). Patients with different onset of HL are characterized by different degree of HL. Profound HL (up to deafness) (in the range from 98 to 108 dB in VFR) is common in patients with juvenile onset of HL while III-IV degree of HL (in the range from 58 to 75 dB in VFR) is detected in the patients having HL with onset in adulthood (Fig. 3). In addition, a comparative analysis of the audiometric data available for proband A-

III2 for six years, from the first audiometry (at the age of 10 years) to the latest (at the age of 16 years), revealed significant deterioration of hearing (from II-III to IV degree of HL) that allowed us to suggest the progressive nature of this form of HL (Fig. 4). It is also interesting to note that the majority of patients (6 out of 10) could not determine the possible cause of their HL. They denied the hereditary cause despite the fact that some of them had deaf close relatives (Table 2). Most likely, this fact is due to that hearing problems of these patients began against a background of preserved hearing and developed speech. In addition, 3 cases of observation of a dense eardrum in adult patients are of interest since this peculiarity is mainly found only in children (Table 2).

To confirm the hereditary nature of this postlingual form of HL and ascertainment of its type of inheritance, a segregation analysis was carried out. The segregation frequency (SF), estimated using Weinberg's proband method, was 0.20 and matched the expected one for auto-





somal recessive type of inheritance ( $SF_0 = 0.25$ ) (CI 0.026 - 0.374).

Thus, we revealed 10 patients (mostly Evens) with postlingual bilateral sensorineural form of HL of unknown etiology which inheriting as autosomal recessive trait. Moreover, the distant relationship of the examined patients with postlingual HL living in two villages of the Eveno-Bytantaysky National District of the Sakha Republic may indicate the role of the founder effect in the local prevalence of this pathology.

We hope that the results obtained during this work will allow us not only to further reveal the molecular and genetic cause of postlingual form of HL in examined families, but also to uncover the mechanism of its accumulation in Eveno-Bytantaysky National District of Yakutia.

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## ESTIMATION OF BODY MASS INDEX IN PATIENTS WITH CORONARY HEART DISEASE AGED OVER 60 IN THE CASE OF YAKUTIAN CITIZENS

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### ABSTRACT

An analysis of the body mass index (BMI) revealed the ethnic, gender, age differences among the groups of hospital patients with coronary heart disease (CHD) aged over 60. Significantly higher value of BMI was identified in non-indigenous patients compared to Yakut group that was respective to the obesity of  $p < 0.001$ . Maximum values of BMI were established in the older group aged between 60 and 74 years. The decrease in BMI can be observed with the age in the senile age group and more clearer dependency on age in the indigenous group. When comparing the BMI among the age groups: older, senile age and long-livers, the lower value of BMI was noted among long-livers ( $p < 0.001$ ). The obesity was identified significantly more often among women.

**Keywords:** body mass index, obesity, chronic coronary heart disease, non-indigenous, indigenous (Yakut), older, senile age, long-livers, Yakutia.

**Introduction.** Obesity is an independent risk factor of cardiovascular diseases, including arterial hypertension, coronary heart disease and heart failure, and is related to the increased risk of morbidity and mortality [4]. The prevalence of obesity increases with age [6] and there is enough evidence to consider the decrease in body mass as an important action preventing cardiovascular, endocrine and other diseases. The obesity is common among the patients with CHD and higher death rate is observed at values of BMI equivalent  $< 20 \text{ kg/m}^2$  and  $\geq 30 \text{ kg/m}^2$  [5]. Epidemiological studies have proven the overweight and obesity to be the risk factors of increased human mortality [7].

**The purpose of study** - the examination of overweight and obesity prevalence on BMI in the group of patients with CHD aged 60 and older living in Republic of Sakha (Yakutia).

**Material and research methods.** The research included 354 patients under the age of 60 and older with verified diagnosis of CHD, who passed the examination and treatment in cardiological department of Geriatric center, Yakutsk city. The examined population consists of native group - Yakuts (100%) ( $n=205$ , average age  $77.6 \pm 0.6$ ) and European group - Russians (91.3%), Ukrainians, Tatars and Germans (8.7%) ( $n=149$ , average age  $75.5 \pm 0.7$ ). The studied groups were

divided based on gender - men ( $n=187$ ) and women ( $n=167$ ), age - older (from 60 to 74 years old,  $n=154$ ), senile (from 75 to 89 years old,  $n=149$ ) and long-livers (90 years and older,  $n=51$ ) (WHO, 1963). Body mass index (BMI) or Quetelet II index was used to assess the ration of weight and height. BMI was calculated using the following formula:  $\text{BMI (kg/m}^2\text{)} = \text{weight (kg)/height (m}^2\text{)}$ . Body weight was considered excessive with the BMI of  $\geq 25 \text{ kg/m}^2$ , and the presence of obesity was indicated with the BMI value of  $\geq 30 \text{ kg/m}^2$  (European Guidelines for the III review, 2003).

The research was conducted as part of research work program "The contribution of metabolic syndrome to the development of coronary arteries atherosclerosis among Yakutian residents" of Yakut Science Center of Complex Medical Problems and was approved by the local committee on biomedical ethics at the YSC CMP. All the surveyed voluntarily gave the approval to take part in biomedical research.

Statistical processing of the results was performed using the methods of parametric and non-parametric statistics. Student's t-criterion was used to assess the intergroup differences in the values of indicators with the continuous distribution and Pearson's  $\chi^2$ -criterion was applied for the comparison of the frequency values. Methods of multiple intergroup

differences, namely Kruskal - Wallis H-test and single-factor analysis of variance (ANOVA) were also used. The analysis of the dependence between the indicators was performed using the Pearson r-test, Spirmen's rs-test and the Pearson  $\chi^2$ -criterion. Statistical processing of the material was carried out on a computer using the standard software package of the statistical analysis (Statistica for Windows, v. 6.0). The critical level of validity of the null statistical hypothesis (about the absence of significant differences or factorial effects) was taken as 0.05.

**Results and discussions.** The probability of the development of cardiovascular disease increases with the rise of BMI [8]. Higher BMI was found in non-indigenous group compared with Yakut group (Table 1).

The estimation of BMI in patients (aged from 60 to 106 years old) revealed more frequent presence of obesity ( $p < 0.001$ ) in non-native patients while Yakut group had normal BMI ( $p < 0.001$ ) (Table 2).

An analysis of the dependence of BMI on age, taking into account ethnicity, was carried out in order to monitor the amount of body weight with age. It has been revealed that BMI decreases with age and most significantly traced in the Yakut group compared with non-indigenous people ( $r = -0.27$ ,  $p < 0.001$  and  $r = -0.16$ ,  $p = 0.058$ , respectively) (Figure 1).

The significant decrease in BMI was



detected when comparing the BMI values of older, senile age groups and long-livers regardless to ethnicity (Table 3).

By the age of 90 years and older, the majority (80.4%) of long-livers have a normal body weight – significantly more often than the older (36.9%) and senile age groups (37.0%); they were significantly less likely to be overweight and obese. The maximum values of BMI in the examined patients were found in the group of older people aged between 60 and 74 years (Table 4).

Statistically significant differences in BMI ( $\chi^2 = 33.68$ ;  $p < 0.001$ ) were found between the groups of patients of older, senile age and long-livers (Table 4).

Applied non-parametric Kruskal-Wallis test and univariate analysis of variance for the determination of the value of BMI revealed statistically significant differences in BMI in the group of men and women (Table 5).

The highest BMI is significantly more often registered in the older group among women, compared with representatives of other age groups.

Significantly lower values of body mass and BMI were established in men among long-livers compared with men of older and senile age ( $H = 11.97$ ;  $p = 0.003$  and  $H = 10.15$ ;  $p = 0.007$ , respectively). In the group of women significantly lower body weight and BMI were also found among long-livers ( $H = 23.68$ ;  $p < 0.001$  and  $H = 19.79$ ;  $p < 0.001$ , respectively).

Similar indicators were obtained in the Khanty-Mansiysk Autonomous region as a result of a study of 109 long-livers having cardiovascular pathology. The age of long-livers at the time of the survey was 90-101 years [2].

it was noted that a large proportion of men and women have normal body weight (44.9%; 41.3%, respectively) when evaluating the BMI of men and women, without regard to ethnicity and age, (Table 6).

At the same time, women are significantly more likely to have obesity than men (25.7% and 13.4%, respectively;  $\chi^2 = 7.93$ ;  $p < 0.005$ ), and their BMI is higher than in men ( $\chi^2 = 9.11$ ;  $p = 0.011$ ) (see Table 6).

Similar results were also obtained in the works of other researchers while identifying ethnic differences in BMI, where the most common BMI corresponding to obesity was found among the non-native population compared to the native and in the group of women unlike men [1, 3].

**Conclusions.** 1. Significantly higher BMI values corresponding to obesity were found in patients of non-native nationality compared to Yakut group of patients.

Table 1

The value of BMI in both native and non-native group of patients with CHD aged 60 and older (n=354)

Indicator	Population		t	p	z *	p
	non-native (n=149)	native (n=205)				
BMI, kg/m <sup>2</sup>	27.3±0.4	25.0±0.3	4.57	<0.001	4.38	<0.001

\* - z-approximation for the non-parametric Wilcoxon-Mann-Whitney U-test

Table 2

The estimation of BMI in non-native patients with CHD aged 60 and older (n=354)

BMI, кг/м2	Population				X <sup>2</sup>	p
	non-native (n=149)		native (n=205)			
	abs.	rel., %	abs.	rel., %		
18.5–24.9	48	32.2	105	51.2	11.94	<0.001
25.0–29.9	60	40.3	74	36.1	0.47	>0.10
30.0 and more	41	27.5	27	13.2	10.54	<0.001

Note: BMI < 18,5 кг/м<sup>2</sup> – body mass deficit; 18,5–24,9 кг/м<sup>2</sup> – kg/m<sup>2</sup> – normal; 25,0–29,9 кг/м<sup>2</sup> – excessive body weight; ≥ 30,0 кг/м<sup>2</sup> – obesity.

Table 3

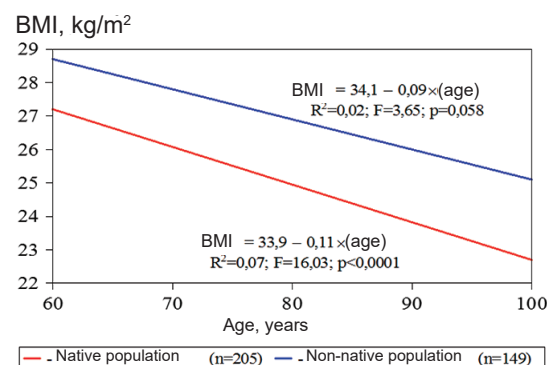
The value of BMI in the non-native and Yakut groups of patients of older, senile age and long-livers with CHD (n=354)

Indicator	Age (years)			H	p	F	p
	60–74 (n=154)	75–89 (n=149)	≥90 (n=51)				
BMI, kg/m <sup>2</sup>	26,8±4,8	26,3±3,8	23,4±2,8	30,60	<0,001	13,23	<0,001

2. The maximum values of BMI are established in the older group (between 60 and 74 years old). Significantly lower BMI is found among long-livers compared with the older and senile age groups.

3. The decrease in BMI is observed with age and is more pronounced in the Yakut group, in the non-native group there is only a tendency to the decrease in body weight.

4. Obesity is significantly more common in women than in men.



Dependence of BMI on age in non-native and Yakut patients with CHD aged 60 years and older (n=354)

Table 4

The estimation of BMI in older, senile age groups and long-livers with CHD (n=354)

BMI, kg/m2	Age, years						X²	p
	60–74 (n=154)		75–89 (n=149)		90 and more (n=51)			
	абс.	отн., %	абс.	отн., %	абс.	отн., %		
18.5–24.9	57	37.0	55	36.9	41	80.4	33.55	<0.001
25.0–29.9	63	40.9	63	42.3	7	13.7	14.50	<0.001
30.0 and more	34	22.1	31	20.8	3	5.9	6.90	=0.032

Note:  $\chi^2=33,68$ ;  $p<0,001$ .

Table 5

The BMI value in the non-native and Yakut group of men and women with CHD aged 60 years and older (according to the results of the Kruskal-Wallis test and single-factor analysis of variance) (n=354)

Age, years	Gender				H	p	F	p
	men n=187)		women (n=167)					
	n	M±m	n	M±m				
60–74	83	25.9±0.4	71	27.8±0.7	30.60	<0.001	13.23	<0.001
75–89	79	25.9±0.4	70	26.8±0.5				
90 and older	25	23.7±0.5	26	23.0±0.6				

Table 6

The estimation of BMI in men and women with CHD aged 60 and older (n=354)

BMI, kg/m2	Gender				$\chi^2$	p
	men (n=187)		women (n=167)			
	abs.	rel., %	abs.	rel., %		
18.5–24.9	84	44.9	69	41.3	0.33	>0.10
25.0–29.9	78	41.7	55	32.9	2.54	>0.10
30.0 and more	25	13.4	43	25.7	7.93	<0.005

Note:  $\chi^2=9.11$ ;  $p=0.011$ .

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## SEROLOGICAL AND MOLECULAR-BIOLOGICAL VERIFICATION OF VIRAL HEPATITIS B, C, D AND E IN VARIOUS POPULATIONS OF THE REPUBLIC SAKHA (YAKUTIA)

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## ABSTRACT

The **purpose** of the study is the serological and molecular-biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

**Materials and methods.** Used official statistics and annual reports. The analysis of the incidence of acute and chronic viral hepatitis B and C, hepatitis carriers for the period from 1999 to 2016, as well as serological and molecular biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

**Results and discussion.** In the dynamics of the incidence of AVG B, the carriage of VGV and VG C in Yakutia, there is no existence of any of their own laws that are not inherent in many regions of Russia. In general, based on the level and dynamics of the incidence of chronic viral hepatitis In the country, it is possible to characterize the overall epidemiological situation as unfavorable, even despite a noticeable decrease in the incidence. The unstable undulating nature of the incidence and their increase in recent years indicate the persistence of epidemiological tension with respect to viral hepatitis B. A distinctive feature of the structure of chronic viral hepatitis in the Republic of Sakha (Yakutia) is the high incidence of chronic viral hepatitis B and the steady growth of chronic viral hepatitis C. The infection of the population of the Republic with hepatitis B and C viruses can be determined as high. This situation, given the high frequency and severity of the adverse effects of HBV, HCV infections, as well as the endemicity of HDV infection, poses a threat to public health. According to the results of serological, molecular biological studies, a high incidence and infection rate of the population of the republic with all known hepatitis viruses was stated. An increased circulation of hepatitis E virus, previously considered a tropical infection, was also detected in the Arctic zone of Russia.

**Conclusion.** In general, an epidemiological analysis of the incidence of acute and chronic viral hepatitis showed that in the Republic of Sakha (Yakutia) a highly endemic area with respect to viral hepatitis C, B, D and E, and such a tense epidemiological situation requires urgent appropriate measures. Studies of the genetic heterogeneity of the identified hepatitis viruses and the pathogenetic mechanisms of the development of the disease among the indigenous people of the Russian North are also required.

**Keywords:** acute hepatitis B and C, chronic hepatitis B and C, hepatitis D, hepatitis E, HBsAg, HBV DNA, a-HCV, HCV RNA, a-HDV, a-HEV.

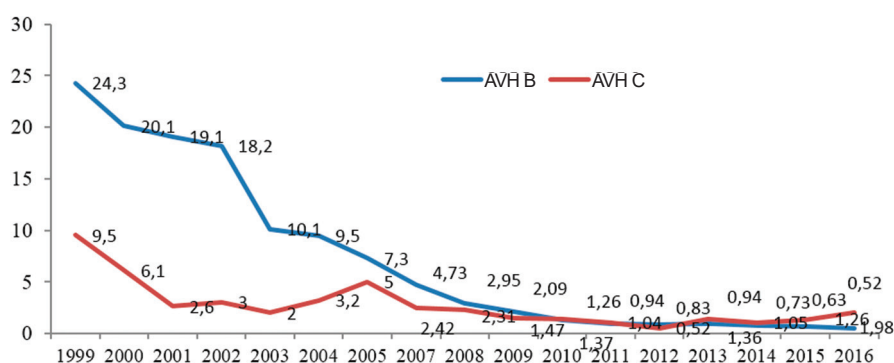
**Introduction.** In recent years, the epidemic process of parenteral viral hepatitis B, C and D in the world and Russia is changing. There is a sharp decline in the prevalence of acute forms of viral hepatitis B and D, which is associated with the widespread use of vaccine prevention of viral hepatitis B. However, the proportion of chronic hepatitis B in the overall structure of chronic viral hepatitis in Russia, in particular, in the Republic of Sakha (Yakutia) remains [1, 19]. Against the background of a decrease in the incidence of viral hepatitis B, the prevalence of the incidence of chronic viral hepatitis C is commonly observed [21, 9, 3]. It is especially relevant for Yakutia to study the patterns of the spread of infection caused by viral hepatitis D. Earlier studies have shown an extremely high frequency of detection of antibodies to the hepatitis D virus in different regions of the country [17, 7, 5].

Hepatitis E is an important public health problem throughout the world and by some estimates, one third of the world's population is infected with HEV infection [18]. Studies show the widespread prevalence of viral hepatitis E. Mainly it manifests itself in an outbreak of acute hepatitis in tropical, subtropical countries [2, 4, 8]. In many European countries, the detectability of serological markers of viral hepatitis E among donors varies from 1.3% in Italy to 52% in France, and in risk groups among farmers and hunters this range varies from 1.3% to 52% [12, 15].

Russia is considered a non-endemic region for hepatitis E, especially the northern territories. Often, HEV infection is found in immunosuppressed patients who may have a delay or absence of a pronounced humoral immune response to the infection [6]. Recent studies have shown that viral hepatitis E is not only an anthroponotic disease, as previously thought, but may also be zoonanthroponotic [13]. Moreover, genotypes 1 and 2 cause disease in humans, and genotypes 3, 4 - in various wild and domestic animals (pigs, cows, horses, deer, dogs, ducks) [20, 11, 14, 10, 15].

**The aim of the study** is the serological and molecular-biological monitoring of the latitude of viral hepatitis B, C, D and E in the Republic of Sakha (Yakutia).

**Methods and materials of the research.** To study the incidence of acute and chronic viral hepatitis B and C in the Republic of Sakha (Yakutia), data of official statistics, annual reports of the Republican Center of Rospotrebnadzor were used. The analysis of the incidence of acute and chronic viral hepatitis B and C, and the carriage rates of hepatitis B



**Fig.1.** Dynamics of the incidence of acute forms of viral hepatitis B and C in the period from 1999 to 2016 (figures per 100,000 population)

from 1999 to 2016 have been carried out.

Serological and molecular biological studies were carried out in two groups of the population of the Republic. The first group consisted of "conditionally healthy" people in the amount of 71 people, of whom 13 were men (18.3%) and 58 were women (81.7%). The average age of the subjects was 41.6 years (the median of the age of the conditionally healthy was 42 years, the range was 12-65 years, the interquartile range was 35-53 years), while the median age of men was 39 years old with an interquartile range of 32-45 years women - 43.5 and 32-53, respectively; no statistically significant age differences were found by sex ( $Z = 0.85$ ;  $p = 0.39$ ). The second group (group II) included 78 patients with various etiological forms of viral hepatitis (B, C and D), among whom there were 24 men (30.7%) people, women - 54 (69.3%). The average age of patients was 50.3 years (the median age of patients was 52 years, the range was 28-83 years, the interquartile range was 43.5-59 years), the median age of men was 49 years old with an interquartile range of 41-58 years, women - 53 and 45-60 respectively; in this group of subjects, there were also no statistically significant differences in age by gender ( $Z = 0.92$ ;  $p = 0.36$ ).

By ELISA studies were performed for the presence of HBsAg, a-HBsAg (mU / ml), a-HBc-total, a-HBs IgM, a-HBeAg, a-HBe IgG, a-HDV, a-HDV-IgM, a-HCV, a-HEV-IgG. For detection of viral hepatitis markers, Gepascan HBsAg and Gepascrin test systems were used, manufactured by Bioservice, Moscow, Vektogep D - antibodies-strip, manufactured by Vector-Best, Novosibirsk, Anti -HBc EIA »Cobas Core, Hoffmann La Roche (Switzerland). Anti-HBs were quantified using the anti-HBs Quant EIA II Roche ELISA test system on a Cobas Core II automatic analyzer from Hoffmann La Roche (Switzerland). HCV-quantitative RNA was isolated by PCR, followed by HCV genotyping, HBV-quantitative DNA,

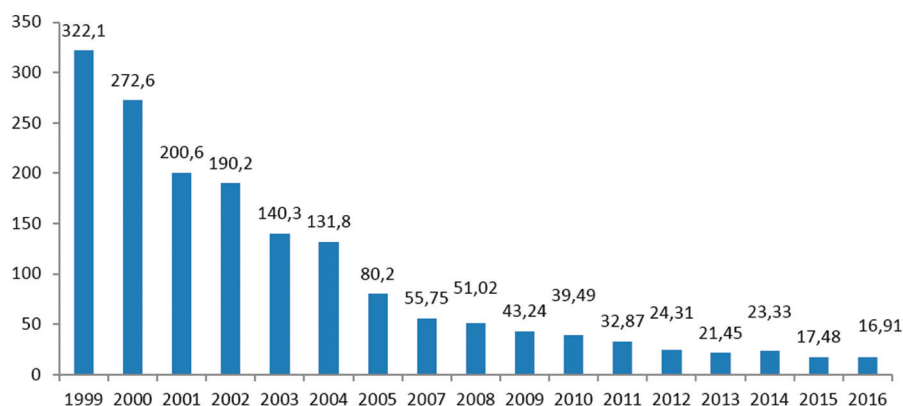
HDV-qualitative RNA. Statistical analysis of laboratory results was performed using Statistica 8.0 statistical software package.

**Results and discussion.** In the Republic of Sakha (Yakutia), the epidemiological situation regarding acute viral hepatitis has now improved significantly (Fig. 1). The incidence of acute hepatitis B from 1999 to 2002 was characterized by a gradual decrease in indicators from 24.3 per 100 thousand to 18.2, then there was a sharp decline in 2003 to 10.1 per 100 thousand people, followed by a gradual decrease in up to 0.53 per 100 thousand population. In 2014, only 7 cases of acute hepatitis B were registered in the republic, in 2015 and in 2016, 6 and 5 cases, respectively.

In the dynamics of hepatitis B virus infection, there is a markedly noticeable trend of a sharp decrease in infection of the population with the hepatitis B virus (Fig. 2). This is due to the implementation of preventive work against hepatitis B. The level of virus-carrying indicators in 1999 was 322.1 per 100 thousand population, which was significantly higher than the average level of the all-Russian indicator. This exceptionally high level exceeded the average Russian figure by about 3 times. In 1999, the virus infection rate in the Russian Federation was 88.0 per 100 thousand people. A decrease in virus infection rates of more than 19 times in 17 years (from 322.1 to 16.91 per 100 thousand people) indicates a significant breakthrough effect of preventive work and a high efficacy of hepatitis B vaccination, especially with the introduction of hepatitis B vaccination. The national calendar of prophylactic vaccinations in 2002, which pledges three-time vaccination of newborns against hepatitis B according to the scheme 0-6-12 (the first 12 hours of life - 6 months - 12 months).

The incidence rate of acute hepatitis C in 1999 was 9.5 per 100 thousand people (Fig. 1). In subsequent years, there was a decline in indicators to 2.0 per 100





**Fig.2.** The long-term dynamics of the decrease in the carriage of hepatitis B (figures per 100,000 population)

thousand population in 2003 and a slight increase in indicators to 5.0 in 2005.

Since 2007, there has been a gradual steady decline in the incidence of acute viral hepatitis to 0.52 per 100 thousand people in 2012. Moreover, in 2008-2012, the incidence rates of acute viral hepatitis B and C were compared and amounted to 1.0-2.0 per 100 thousand people. Since 2013, there has been a change in the epidemiological situation with respect to acute viral hepatitis B and C. The incidence of acute viral hepatitis B continues to decline gradually, reaching 0.52 per 100 thousand people in 2016. At the same time, the incidence of acute viral hepatitis C gradually, steadily increases from 1.36 in 2013 to 1.98 per 100 thousand people in 2016. It should be noted that in recent years an unfavorable situation has been created for viral hepatitis C, there is a tendency to an increase in the incidence rate, prevailing over acute hepatitis B.

Thus, in the dynamics of the incidence of AVH B, the carriage of VGV and VG C in Yakutia, there is no existence of any own patterns that are not inherent in many regions of Russia.

The dynamics and incidence of chronic forms of viral hepatitis B and C are significantly different from acute forms. From 1999 to 2013, the incidence rates of chronic hepatitis B rose steadily, and significantly, due to improved diagnostics and the widespread introduction of immunological laboratories in health care facilities, mandatory testing for the first time applied for a viral hepatitis marker - HbsAg. The epidemiological situation in relation to chronic hepatitis B is the same as in acute hepatitis B: with the maintenance of hepatitis B vaccination in the national immunization schedule since 2003, a decrease in incidence has been observed.

The decrease in the incidence of chronic hepatitis B was undulating. The maximum incidence rates of chronic hep-

atitis B were at 63.3 per 100 thousand population in 2003, the minimum decrease to 33.13 in 2007. In recent years, there has been a trend of a moderate steady increase from 27.83 per 100 thousand people in 2013 to 37.15 per 100 thousand people in 2016.

In general, based on the level and dynamics of the incidence of chronic viral hepatitis B in the country, it is possible to characterize the overall epidemiological situation as unfavorable, even despite a marked decrease in the incidence. The unstable undulating nature of the incidence and their increase in recent years indicate the persistence of epidemiological tension with respect to viral hepatitis B. Against the background of a general decrease in the incidence of hepatitis B, the incidence of viral hepatitis C increases. 13 per 100 thousand population for chronic hepatitis C versus 37.15 chronic hepatitis B in 2016). This tendency is observed everywhere, since there is no specific prophylaxis for viral hepatitis C (Fig. 3).

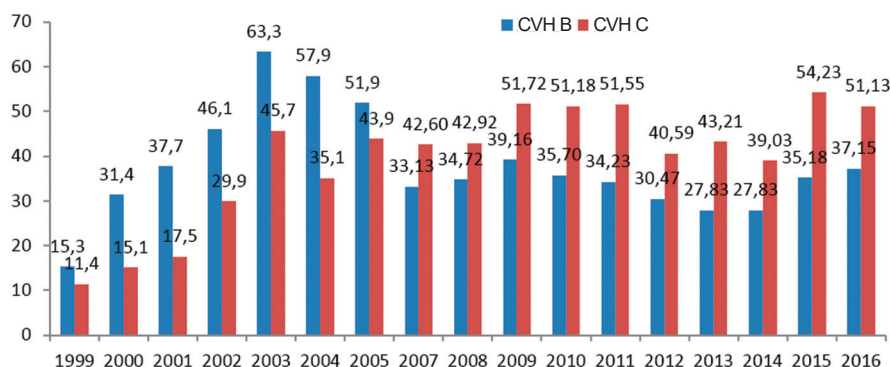
In order to detect infection of the population with hepatitis B, C, D, and E viruses, selected groups studied serological and molecular biological markers with the aim of etiological verification, as well as determining the virological activity of the pathological process. The total results of

the studies in both selected groups for the study are shown in Table 1.

Analysis of the results of detection of markers of viral hepatitis B, C, D and E according to serological studies showed a high intensity of the course of the epidemic process of viral hepatitis among various population groups of the Republic of Sakha (Yakutia). Analysis of the presented studies found that among the population of the republic there is a high proportion of seropositive individuals for all viral hepatitis with the highest rates of hepatitis C in the group of patients (I group) up to 71.8%, hepatitis B up to 24.3% and hepatitis E up to 23, 0% of cases. High infection of HBsAg-positive individuals with hepatitis D virus markers (a-HDV — 42.1%) was particularly alarming.

For the purpose of diagnostic verification in the group of patients with viral hepatitis, he was examined for hepatitis B virus markers (Table 1). The main marker of viral hepatitis B HBsAg was detected in a quarter of patients (24.3%). At the same time, out of 19 HBsAg-positive patients, HBV DNA was detected in 13 patients, which was 68.4%, which indicates an increased replicative activity of virus B. Moreover, a quantitative analysis of HBV DNA showed an average viral load of  $2.6 \times 10^4$  copies / ml the maximum indicators  $3.1 \times 10^2$ , with the minimum -  $1.7 \times 10^4$ . These patients require long-term systematic treatment, regular follow-up, taking into account clinical manifestations, biochemical and serological indicators.

In group I, HBsAg was detected in 9.8% of the subjects. Of 7 HBsAg-positive people, HBV DNA was detected in 5 (71.4%). Moreover, the viral load of HBV DNA was higher than in the group of patients, and the rates ranged from  $1.9 \times 10^2$  to  $3.0 \times 10^2$ . Hepatitis B markers, such as a-HBeAg IgG and a-HBcor-cumulative, were found in 21.1 and 28.1% of cases, respectively, which are now estimated to be a sign of chronic latent HBV infection.



**Fig.3.** Dynamics of incidence rates of the registered forms of chronic viral hepatitis B and C in the Republic of Sakha (Yakutia) in the period from 1999 to 2016

The significantly high detection rate of a-HBc IgG in both groups of patients also indicates a history of acute hepatitis B, the presence of chronic hepatitis B, and the carriage of HbsAg.

One of the aspects of HbsAg-positive viral hepatitis, which cause worsening of the disease and a high degree of chronicity, is the addition of HDV infection. In the group of patients, the proportion of a-HDV among HBsAg positive was 42.1%, and the marker of replicative activity, showing active viral replication, a-HDV IgM was detected in 10.5% of the studied (Table 1). The identified indicators of the presence of hepatitis D virus markers in the structure of chronic viral hepatitis are unprecedentedly high in the Republic of Sakha (Yakutia). Usually HDV infection is registered in 5-7% of cases in the European part of Russia.

Of particular concern is the fact that the hepatitis D virus causes, as a rule, very severe forms of chronic hepatitis, which in a short time lead to cirrhosis of the liver. It is necessary to note the alarmingly high proportion of HDV infection in the structure of chronic viral hepatitis 42.1%, which indicates an obvious increase in the intensity of the epidemic process in recent years of viral hepatitis B in the territory of Yakutia.

In Yakutia, as well as throughout the country, the proportion of the incidence of viral hepatitis C is increasing and prevailing over the incidence of viral hepatitis B. In the study of the breadth of prevalence in patients with chronic hepatitis and healthy individuals, the serological markers of viral hepatitis C (a-HCV) were detected in most patients and accounted for 71.8%. Among conditionally healthy individuals, this indicator was 12.6%, while HBsAg in this group was detected in only 9.8% of cases. The wide distribution of a-HCV and the core, NS3, NS4, NS5 spectrum among patients and the high proportion of hepatitis C virus (HCV RNA) detected in seropositive individuals among patients and conditionally healthy 67.8% and 77.7%, respectively, indicates a significant intensity Hepatitis C epidemic process among the population of the republic. (Table 1). The group of conditionally healthy individuals consisted of the studied, not belonging to the groups at high risk of infection with viruses of parenteral hepatitis. The detection of up to 71.4% of HBV DNA and 77.7% of HCV RNA in seropositive, conditionally healthy subjects indicates a high activity of viral B and C infections in the studied population.

Thus, the infection of the population of the republic with hepatitis viruses B and C can be defined as high. This situation,

Table 1

### Serological and molecular biological markers of viral hepatitis B. C. D. E among various population groups (n-149)

VG markers	Number of examinations	Sick		Number of examinations	Conditionally healthy		Chi-apt.	p
		n	%		n	%		
Markers of viral hepatitis B								
HBsAg	78	19	24.3	71	7	9.8	5.4	0.02
a-HBsAg*		21	26.9		35	49.2	7.9	
a-HDcor-суммарные		42	53.8		20	28.1	10.1	0.002
HBeAg		0	-		0	-		
a-HBeAg IgG		34	43.5		15	21.1	8.5	0.004
ДНК HBV**	Of 19 HBsAg positive	13	68.4		5	7.0	6.7	0.01
Markers of viral hepatitis D								
a-HDV IgM	Of 19-HBsAg	2	10.5	Of 19-HBsAg	0	-		
a-HDV	positive	8	42.1	positive	0	-		
Markers of viral hepatitis C								
a-HCV	78	56	71.8	71	9	12.6	52.8	<0.001
core	Of 56 HCV positive	12	21.4	Of 9 HCV positive	1	1.4	10.0	0.002
NS3		10	17.8		0	-		
NS4		7	12.5		0	-		
NS5		6	10.7		0	-		
PHK HCV***		38	48.7		7	77.7		
Markers of viral hepatitis E								
a-HEV IgG	78	18	23.0	71	14	25.3	0.3	0.6

Note: a-HBsAg \* - quantitative analysis on average 122.09 MU / ml. maximum indicators -> 263.9 MU / ml. minimum - 12.7 MU / ml

HBV \*\* DNA - quantitative analysis of an average of  $2.6 \cdot 10^4$ . the maximum of  $3.1 \cdot 10^2$ . the minimum -  $1.7 \cdot 10^4$

HCV \*\*\* RNA - quantitative analysis of an average of  $2.6 \cdot 10^4$ . the maximum performance of  $7.0 \cdot 10^4$ . the minimum -  $5.4 \cdot 10^2$

given the high frequency and severity of the adverse effects of HBV, HCV infections, as well as the endemicity of HDV infection, poses a threat to public health.

The viral hepatitis E endemic to tropical countries in the republic was not subject to testing for patients with hepatitis, as well as during monitoring studies. Our studies showed a high circulation of the E virus among conditionally healthy and sick VH - 25.3% and 23.0%, respectively. In addition, patients with acute viral hepatitis with unclear etiology may have cases of acute viral hepatitis E, which is currently not routinely diagnosed in Russia in routine practice.

In connection with the detection of serological markers of hepatitis E in domestic and wild animals, which can be food of the population, these animals can be a source of infection of acute hepatitis E, which can be especially dangerous for pregnant women.

Our further studies have shown that the serological and molecular biological characteristics of chronic hepatitis B and

C in the country are distinguished by an increased replicative activity of viruses in more than 3/4 of patients and a high degree of infection by 2, 3, and even 4 other viruses. hepatitis at the same time (mixt infection). So among 19 patients with chronic hepatitis B, hepatitis C markers were found in 31.5% of cases, while the virus (HCV RNA) was detected in 21.0% of cases. Anti HEV IgG was detected in 21.0% (4 of 19). A similar situation occurs in patients with chronic viral hepatitis C. Among 68 patients with chronic hepatitis C, markers of hepatitis B (HBsAg), hepatitis D, and hepatitis E are often detected (in fact, a fourfold infection (HCV + HBV + HDV + HEV) in 11.7% , 4.4% and 25% of cases, respectively (table 2).

Thus, according to the results of serological, molecular-biological studies, a high incidence and infection of the population of the republic with all known hepatitis viruses was stated. An increased circulation of hepatitis E virus, previously considered a tropical infection, was also detected in the Arctic zone of Russia.

Table 2

### 4-fold infection (HBV + HCV + HDV + HEV) among patients with chronic hepatitis B (n-19) and C (n-68). in %

Patients	HBsAg	a-HBcor amounts	a-HBe IgG	DNA HBV	a-HDV	a-HCV	PHK HCV	a-HEV IgG
Hepatitis B	84.2	100.0	68.4	57.8	1.4	31.5	21.0	21.0
Hepatitis C	11.7	45.5	35.3	7.3	4.4	97.0	57.3	25.0

## Conclusion

In general, an epidemiological analysis of the incidence of acute and chronic viral hepatitis showed that in the Republic of Sakha (Yakutia) a highly endemic area with respect to viral hepatitis C, B, D and E, and such a tense epidemiological situation requires urgent appropriate measures. Studies of the genetic heterogeneity of the identified hepatitis viruses and the pathogenetic mechanisms of the development of the disease among the indigenous people of the Russian North are also required.

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## HEALTHY LIFESTYLE. PREVENTION

M.S. Avdeeva

## PHYSICAL DEVELOPMENT AND PHYSICAL FITNESS OF 7-8-YEAR-OLD GIRLS WITH PECULIARITIES OF PERINATAL DEVELOPMENT PERIOD

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## ABSTRACT

**Aim.** The purpose of the research is to study the characteristics of the physical development of 7-8-year-old girls with non-physiological perinatal period.

**Materials and methods.** 236 girls of 7-8-year-old girls from Kirov (Russia) were divided into groups: group I - control (n = 60, physiological perinatal period), group II (n = 58, late gestational hypertension in the anamnesis), group III (n = 61, placental insufficiency in the anamnesis), group IV (n = 57, maternal anemia in the anamnesis). We measured their physiometric characteristics (heart rate, blood pressure, vital capacity of lungs, flexion muscle strength of the right and left hand, maximum oxygen consumption) and anthropometric ones (length, body weight, chest circumference, its excursion). Then the corresponding indices and coefficients were calculated.

**Results.** Girls with late gestational hypertension have lower mass-growth index, the Quetelet index and dynamometry indicators; girls with placental insufficiency have higher systolic blood pressure and lower work power; girls with maternal anemia in the anamnesis have low mass-growth index, the Quetelet index and the power of work.

**Conclusion.** It is shown that the studied perinatal pathologies have a similar remote effect on physical development: gestational hypertension and anemia of a mother during pregnancy affect the mass-growth index and the Quetelet index, placental insufficiency and anemia influence the work power. Thus, we consider these indicators of 7-7-year-old girls (mass-growth index, the Quetelet index and work power) to be the most sensitive to pathologies of the perinatal period.

**Keywords:** physical development, perinatal period pathologies, gestational hypertension, placental insufficiency, pregnancy anemia.

**Introduction.** A number of studies have shown that complications of the perinatal period negatively affect the morphophenotype and adaptation of newborns [4], and the sexual development of adolescents [5]. The increase in the period of gestation is connected with an increase in body mass and its index in adulthood, especially among girls [7].

According to research, gestational hypertension in the anamnesis affects the physical development of children. Children with a gestational hypertension (n = 343) have a higher body mass index and a greater circumference of the chest than those with a physiological perinatal period [6]. The research [22], which aimed to identify the relationship between gestational hypertension of mother and obesity in 4-7-year-old children (n = 88406), showed that mother's increase in pressure by 10 mmHg during pregnancy increases the risk of children's obesity.

In addition, gestational hypertension in the anamnesis affects the state of the cardiovascular system (CVS). A study [16] showed that in 979 children (median age of 7 years) children with gestational hypertension of mother had a higher systolic blood pressure. Also, Tenhola S and co-authors [19] write about higher systolic and diastolic blood pressure of 12-year-old children with a mother's gestational hypertension in the anamnesis, the cause of it may be the elevated concentration of adrenaline in children's blood. In addition to high systolic blood pressure, children with gestational hypertension have a higher level of triglycerides in the blood plasma, which confirms the presence of a metabolic syndrome [17]. According to Alsnes I.V. et al. [6], all children with a

mother's gestational hypertension are at risk for cardiovascular disease.

In addition to gestational hypertension, placental insufficiency has a distant influence on the state of children's CVS. It causes an increase in blood pressure [20] and has a long-term effect on the CVS status [14]. Moreover, placental insufficiency remotely reduces memory [10] (when a child is 12).

In addition to the above pathologies, the mother's anemia during pregnancy has a remote negative impact on the health of children. A study of 78,923 women showed that if a mother had anemia (hemoglobin concentration in the blood was 70-99 g/l), then the risk of anemia of 3-5-year-old children increased [21]. Mother's anemia during pregnancy affects the motor abilities of 1-year-old children [9]. In addition, it has an inverse correlation with the Tiffno-Pinelli index of 8-9-year-old children, i.e. they have a smaller airway patency [18] up to 10 years old [13].

The **purpose** of our study is to study the characteristics of the physical development of 7-8-year-old girls with non-physiological perinatal period.

**Materials and methods of the research.** In retrospect, according to the data of the registration form No. 112-U "The history of the development of the child" and 026/u "Medical card of the child" we studied the perinatal period development of 236 first-year schoolgirls in the city of Kirov (Kirov region, Russia). Girls were divided into 4 groups: I - control (n = 60, physiological perinatal period), II (n = 58, late gestational hypertension), III (n = 61, placental insufficiency), IV (n = 57, maternal anemia in the

anamnesis). Groups II-IV included children with only one of these pathologies. To measure the physical development of girls, physiometric and anthropometric indicators were measured logically: at the beginning of the first grade (1<sup>st</sup> measure in October), in the middle (2<sup>d</sup> measure in January), at the end (3<sup>d</sup> measure in May) and at the beginning of the second grade (4<sup>th</sup> measure in September). Anthropometric indicators included measurements of length, body weight, chest circumference, its excursions and the calculation of weight-growth indices: mass-growth, Rohrer, Pignet, Quetelet [8]. According to anthropometric indicators, we compared the increase between measurements 1 and 2 (October-January), 2 and 3 (January-May), 3 and 4 (May-September).

The physiometric parameters were studied in February-March, measuring the heart rate, blood pressure [15], vital capacity of the lungs [11], the flexion muscular strength of the right and left hand [12]. We calculated life and strength index, pulse pressure, coefficient of efficiency of blood circulation, coefficient of endurance [3]. The level of general endurance was assessed by the maximum oxygen consumption (MOC), using the method of indirect calculation of the MOC for power and heart rate during the performance of the test step (climbing the bench at a height of 0.35 m for 4 minutes with a frequency of 20 cycles per minute) [1]. Using the MOC, the level of physical working capacity was assessed according to Apanasenko [2]. The results of the research were subjected to statistical processing using parametric statistics methods in the Microsoft Excel software package on an Intel Pentium computer.

Then the arithmetic mean (M) and the standard error of the mean (m) were calculated. The differences were assessed by the Student's criterion (t) for independent samples, and they were considered reliable at  $p < 0.05$  (in text it is indicated as «\*»).

**Results and discussion.** When compared with the group I (control) for girls from the group II (late gestational hypertension), lower values of weight-growth indices and dynamometry indicators were revealed (Table 1).

The obtained data contradict the literature data on the higher body weight among children with a mother's gestational hypertension in the anamnesis [6, 22]. We have not confirmed the data on the influence of gestational hypertension on the cardiovascular system [16, 17, 19]. For the first time the effect of gestational hypertension on dynamometry was established.

When comparing groups I (control) and III (placental insufficiency), no differences in anthropometric parameters were revealed, but differences in cardiovascular parameters were established (Table 2). The group III has higher systolic blood pressure and lower exercise power.

We have confirmed the literature data on the increase of blood pressure of children with placental insufficiency [14, 20]. For the first time, it has been established that placental insufficiency has a negative effect on the power of the work.

Comparison of the group I (control) and IV (maternal anemia) has revealed differences in three indices (Table 3). The group IV has the lower mass-growth index, the Quetelet index and the work power.

We have not confirmed the literature data on the negative impact of the maternal anemia in the anamnesis on the state of the child's airways [13, 18] - differences in the magnitude of the vital capacity of the lungs, the vital index, the Stange and Gentcha tests between groups I and IV.

For the first time it has been established that anemia has a negative effect on the power of work, the mass-growth index and the Quetelet index, which are the calculation units and indirectly indicate the amount of body weight.

**Conclusion.** While studying 236 girls, we have established a relationship between the features of physical development of 7-8-year-old girls and non-physiological perinatal period. Statistically significant differences were revealed in six parameters, including both anthropometric and physiometric indicators. Regardless of the type of perinatal pathology (gestational hypertension, placental insufficiency, anemia), girls are more likely to have differences in the Quetelet index, mass-

Table 1

Indicators of physical development of the group I (control) and the group II (late gestational hypertension)

Indicators	Measurement №	Control		Late gestational hypertension		p
		M	m	M	m	
Mass-growth index. g / cm	2	206.57	6.02	189.76	3.52	<0.05
Quetelet index. kg / m <sup>2</sup>	2	15.77	0.38	14.67	0.22	<0.05
Dynamometry of the right hand. kg	4	14.20	0.44	12.68	0.63	<0.05
Dynamometry of the left hand. kg	4	13.34	0.48	11.59	0.59	<0.05

Table 2

Indicators of physical development of the group I (control) and the group III (placental insufficiency)

Indicators	Measurement №	Control		Placental insufficiency		p
		M	m	M	m	
Systolic blood pressure. mmHg	-	95.45	1.32	99.81	1.71	<0.05
Working power. kg * m / min	-	227.52	13.31	192.10	5.74	<0.05

Table 3

Indicators of physical development of the group I (control) and the group IV (maternal anemia)

Indicators	Measurement №	Control		Anemia		p
		M	m	M	m	
Mass-growth index. g / cm	3	206.57	6.02	189.63	5.25	<0.05
Quetelet index. kg / m <sup>2</sup>	3	15.77	0.38	14.66	0.30	<0.05
Working power. kg * m / min	-	227.52	13.31	194.17	7.22	<0.05

growth index and work power. All three indicators are calculated and determined taking into account the body weight. Consequently, perinatal period pathologies remotely affect the body weight, reducing its value in comparison with the control at 7-8 years. It should be noted that two pathologies of the perinatal period (gestational hypertension and anemia) affect the mass-growth index and Quetelet index, while placental insufficiency and anemia affect the work power. Thus, we consider these indicators (the mass-growth index, Quetelet index and work power) in 7-8-year-old girls to be most sensitive to perinatal period pathologies.

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## OPINION OF YOUNG PEOPLE ON THE POTENTIAL RISK OF THE BIRTH OF DEAF CHILD

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### ABSTRACT

In Yakutia, the contribution of *GJB2* mutations to the etiology of hereditary deafness is 48.8% and is one of the highest in Asia, due to a significant accumulation of the mutation of the splice site c.-23+1G>A in the *GJB2* gene due to the founder effect in the Yakut population ("age" of mutation ~ 800 years). The results of scientific research in the field of genetic forms of deafness are actively introduced into practice in the form of various test systems of routine DNA diagnostics. However, the bioethical, social and psychological problems arising from the application of these genetic technologies are less well understood than the molecular genetic aspects of deafness. We conducted a questionnaire and a selection of buccal epithelium of 241 people, whose mean age is 21, in order to analyze their opinion on the potential risk of a deaf child's birth and conduct genetic testing for the presence of the mutation c.-23+1G>A in the *GJB2* gene. The frequency of heterozygous carriage of the mutation c.-23+1G>A of the *GJB2* gene among hearing young people (n = 241) in the Yakut population was 10.8%, which is comparable to the previously obtained data. Analysis of data from the questionnaire with genotypes shows that there are no statistically significant differences in the respondents' responses (p>0.05). As a result of the questionnaire, it is shown that most young hearing people think that deafness can be a hereditary disease (62.6%). Most young people assume the possibility of birth of a deaf child from hearing parents (81.33%), but only 2.49% of respondents agree with this risk. Such an answer can be explained by the protective internals of the psyche, when a person assumes the existence of the same risk of the birth of a deaf child in all people, but denies such a possibility in himself.

**Keywords:** opinion of young people, *GJB2* gene, c.-23+1G>A mutation, frequency of heterozygous carrier.

**Introduction.** In recent years, in connection with the expansion of the pos-

sibilities of DNA testing, much attention has been paid to the molecular genetic causes of hereditary forms of deafness. However, at the same time, in many

regions of the world, the bioethical and social aspects of this disease remain insufficiently studied. At present, genetic technologies are ahead of the informa-

\* - Equivalent contribution of authors



tion space, as a result of which there is no formed opinion in Russian society in relation to the heavy moral and ethical issues that entail genetic technologies. Work in this direction was carried out in the United States and a number of European countries [5,6,9], in Russia such studies are practically absent.

Earlier in the Republic of Sakha (Yakutia), the main cause of congenital deafness was identified, which is caused by the mutation c.-23+1G>A in the gene *GJB2* [3]. In the Yakut population, this mutation occurs with an extremely high incidence of heterozygous carriage (10%) [3]. In Yakutia, the contribution of *GJB2* mutations to the etiology of hereditary deafness is 48.8% and is one of the highest in Asia, due to a significant accumulation of the mutation of the splice site c.-23+1G>A in the *GJB2* gene due to the founder effect in the Yakut population ("age" of mutation ~ 800 years) [3,4,11]. The results of scientific research in the field of genetic forms of deafness are actively introduced into practice in the form of various test systems of routine DNA diagnostics. However, the bioethical, social and psychological problems arising from the application of these genetic technologies are less well understood than the molecular genetic aspects of deafness.

In clinical practice, 90% to 95% of deaf children are born in hearing families [7,10]. An analysis of the voices of hearing parents about the possible causes of hearing loss in their child indicates that the majority of hearing respondents in Yakutia (86.1%), Tuva (73.8%) and Bashkortostan (76.2%) do not consider hearing loss in a child hereditary [1, 8]. If we take into account this opinion of the parents, then the hearing loss in their children in 73.8-86.1% of cases is due either to environmental factors or the cause remains unknown [1.8]. At the same time among respondents who participated in the survey, there is a tendency to deny the hereditary nature of the disease in the absence of deaf relatives in the family [1,8]. In this context, the analysis of the opinion of young people about the hypothetical risk of the birth of a deaf child is important from the point of view of forming a reference group of individuals, who for the most part did not face similar moral and ethical problems [1].

The aim of this work is to analyze the opinion of young people about the hypothetical risk of a deaf child's birth.

**Materials and methods.** We conducted a questionnaire and a selection of buccal epithelium in students of the Federal State Autonomous Educational

Institution of Higher Education "North-Eastern Federal University named after M.K. Ammosov ". A total of 241 people took part in the questionnaires, who were students. Of these, 44% were men and 56% women, the average age of participants was 21 years. The urban population was 24%, rural - 74%, did not specify the place of residence / birth - 2%. All the respondents were Yakuts (Table 1).

Questions in the questionnaires were closed alternatives with a choice of one answer option. By completeness of coverage, the questionnaire is selective, conducted among hearing people. By type of contact with respondents - full-time. According to the number of respondents, there is an auditor, that is, the simultaneous filling in of questionnaires by a group of people gathered in the same room in accordance with the rules of a selective procedure. Surveys foreseen by the scope of this research work were carried out after informed written consent of the participants or their parents. The research work was approved by the local committee on biomedical ethics under the YSC of the Commission in 2014 (Yakutsk, minutes No. 41 of November 12, 2014).

Isolation of DNA from the buccal epithelium was carried out by phenol-chloroform extraction. Amplification of fragments of the *GJB2* gene, including exon 1 with 5'-CCGGGAAGCTCTGAGGAC-3' and 5'-GCAACCGCTCTGGGTCTC-3' primers and exon 2 with 5'-TCG-GCCCCAGTGGTACAG-3' and 5'-CTGGGCAATGCGTTAACTGG-3' primers of the *GJB2* gene with flanking regions was performed by PCR. The verification of the amplificate on electrophoresis was carried out in a 2.5% agarose gel and stained with ethidium bromide for 25 minutes. When detecting the mutation of c.-23+1G>A in the *GJB2* gene, we amplified exon 1 of this gene with an intron portion containing a polymorphic restriction site (restriction site - GGTGA (N) 8/7). To do this, the amplified sample with restriction enzyme and buffer was placed in a thermostat for 12 hours at 37 °C and the next day electrophoresis of the amplifications was performed.

### Results and discussion

In this paper, we consider three questions related to the purpose of the study. The first question: "Do you think deafness is a hereditary disease?" Respondents answer: "Yes" or "No". The second question: "Do you think there is a chance of giving birth to a deaf child from hearing parents?". Respondents answer: "Yes" or "No". The third question: "Do you have

**Table 1**  
Data of interviewed young hearing respondents

Young hearing people (n=241)	Number	%
Gender		
Male	106	43.98
Female	135	56.02
Place of residence		
Urban	57	23.65
Rural	178	73.86
No response	6	2.49
Nationality		
Yakut	241	100
Average age – 21		

a chance to give birth to a deaf child?". Respondents answer: "Yes", "No" or "I do not know."

We correlated the respondents' answers about the hypothetical risk of a deaf child's birth with their real risks, by testing their presence of the mutation c.-23+1G>A of the *GJB2* gene, since this mutation among the Yakuts is the most common [11]. The frequency of heterozygous carrier mutation c.-23+1G>A of the *GJB2* gene among hearing young people (n = 241) in the Yakut population was 10.8% (Table 2).

To the question "What do you think, deafness is a hereditary disease?" More than half of the respondents (62.66%) answered "Yes" and 37.34% do not agree with this (Fig. 1 - A). When comparing responses to genotyping data, there were no significant differences in respondents' answers. Thus, heterozygous carriers of the mutation c.-23+1G>A of the *GJB2* gene are larger (76.92%) in the group of respondents who agree that deafness is a hereditary disease, and in a group of those who disagree with this heterozygous carriers of this mutation, 23.08% (Fig. 1-B).

To the question "Do you think there is a probability of giving birth to a deaf child from hearing parents?" The majority (81.33%) consider that hearing parents have such a probability, 17.43% exclude such a possibility and 1.24% did not respond to this question (Fig. 2 - A). In the group of respondents who agree with this probability, heterozygous carriers are larger (88.46%) than in the opposite group (7.69%) (Fig. 2 - B).

To the question "Is there a probability of

**Table 2**  
The frequency of heterozygous carriers of mutation c.-23+1G>A in the gene *GJB2*

	Number (n=241)	%
[wt]; c.-23+1G>A]	26	10.79
[wt]; [wt]	215	89.21

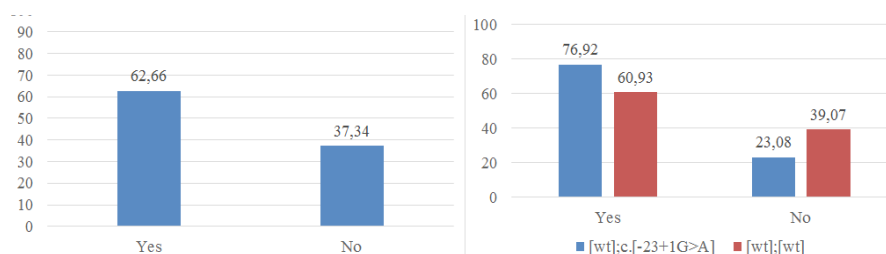
a deaf child's birth?" More than half of the respondents (66.8%) do not know what to answer, they exclude this probability of 29.88% and only 2.49% of respondents agree with this (Fig. 3 - A). When correlating responses with genotypes, it turns out that heterozygous carriers are larger in the group of respondents who do not know whether they have a probability of giving birth to a deaf child (80.77%), less in a group that do not agree with such a probability (19.23%) and in a group, which agreed with this heterozygous carriers was not (Fig. 3 - B).

The carrier frequency of the mutation c.-23+1G>A of the *GJB2* gene among hearing young people ( $n = 241$ ) in the Yakut population was 10.8% (Table 2), which is comparable to earlier data. Earlier in Yakutia, the carrier frequency of mutation c.-23+1G>A, in a population sample of Yakuts of 350 people, was 10.2% [3, 11].

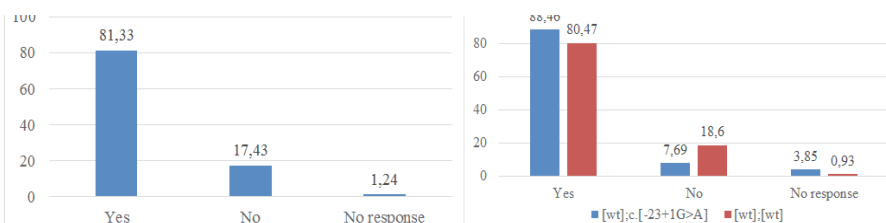
Most young hearing people think that deafness can be a hereditary disease (62.6%) (Fig. 1). In a study conducted among deaf adults and hearing parents of deaf children [1,8], it is shown that these groups think the opposite. That is, most deaf adults (84%) and hearing parents of deaf children (78%) think that their deafness or deafness of their child is a non-hereditary disease [1,8]. The general tendency in denying the hereditary nature of the disease in the study groups is attributed to the respondents' low awareness of the genetic causes of deafness and psycho-emotional reasons - "unwillingness to be guilty of deafness of the child" [1,8]. Consent that deafness can be a hereditary disease among young hearing people may indicate that this group of respondents underestimates the importance of this issue, and is ready to agree with such an abstract statement (that deafness is a hereditary disease). On the contrary, people with hearing loss or having a deaf child / deaf relatives (faced with this problem) are more likely to deny the hereditary nature of hearing loss (78-84%) [8].

It is interesting that most of the young respondents interviewed believe that hearing parents may have a deaf child (81.33%) (Fig. 2), but only 2.49% (Fig. 3) of the respondents agree with this risk. Such a response can also be explained by the protective internals of the psyche, when a person assumes the existence of the same risk of the birth of a deaf child in all people, but denies such a possibility in himself.

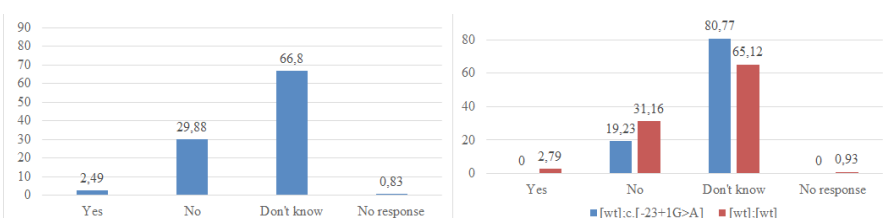
Analysis of the data from the questionnaire with *GJB2* genotypes shows that



**Fig.1.** Answers to the question: «What do you think, deafness is a hereditary disease?»: A - the general distribution of answers; B - the answers of young people in relation to their genotypes.



**Fig.2.** Answers to the question: «Is it possible to give birth to a deaf child from hearing parents?»: A - the general distribution of answers; B - the answers of young people in relation to their genotypes.



**Fig.3.** Answers to the question: «Do you have a chance to give birth to a deaf child?»: A - the general distribution of answers; B - the answers of young people in relation to their genotypes.

there are no statistically significant differences in the respondents' responses ( $p > 0.05$ ). However, heterozygous carriers of the mutation c.-23+1G>A in the *GJB2* gene are more likely (79%) than people without this mutation (60%), agree that deafness is a hereditary disease (Fig. 1-B). To question number 2, "Do you think there is a probability of giving birth to a deaf child from hearing parents?" Heterozygous carriers of mutation c.-23+1G>A are half as rare (7.6%) than people without this mutation (18.6%) answer "no" (Fig. 2-B). In addition, heterozygous carriers of the mutation c.-23+1G>A are uncertain in answering the question about the probability of producing a deaf child in themselves (Fig. 3-B). Such an answer can be explained by the presence of close or distant deaf / hard-of-hearing relatives, and thus carriers of the mutation c.-23+1G>A in the gene *GJB2* assume these risks in themselves. Perhaps, statistical results can be achieved by increasing the sample, and then this trend can be statistically confirmed.

**Conclusion.** Most young people think that a deaf child may be born to hearing parents (81.33%), but only 2.49% of respondents agree with this risk. In heterozygous carriers of the mutation

c.-23+1G>A in the gene *GJB2*, there is a tendency to assume the hereditary nature of deafness more often than in people without this mutation.

#### Acknowledgments

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## ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

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### ANALYSIS OF THE INFECTIOUS SERVICE IN THE REPUBLIC OF SAKHA (YAKUTIA)

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#### ABSTRACT

The main results of the infectious service were analyzed for the study of its state in the Republic of Sakha (Yakutia) during 2000-2017. Also there were given comparative characteristics with analogical indicators in the Russian Federation. According to results of 2017, the growth of morbidity in 12 infections was recorded in the Republic. Due to persisting unfavorable situation, the problem of realization of medical service to infectious patients demands to take system arrangements on deficit reduction of infectious diseases' specialists and infectious beds in hospitals; to increase financing of current medical care in the Republic of Sakha (Yakutia).

**Keywords:** infectious service, morbidity, infectious diseases, personnel, the death rate from infectious diseases.

#### Introduction

The epidemiological situation is intensive in the Republic of Sakha (Yakutia). The spread of the human immunodeficiency virus among the population and an increase in the cumulative number of infected and sick people are continu-

ing; tuberculosis indicators have a steady downward trend. However, comparing with the average of Russian indicators, they continue to keep a sufficiently high level. The incidence of acute respiratory viral infections in the Republic of Sakha (Yakutia) is higher than the incidence rate

in the Russian Federation by 45%, in the Far Eastern Federal District by 50%. Last two years expansion of the incidence of whooping cough and enterovirus infection is noted in the Republic, which is connected with contiguous cyclical rise in the incidence rate. In 2017, the incidence



rate of acute viral hepatitis in the country is 18.5% higher than last year, which is caused by an increase in the incidence of viral hepatitis A 3.9 times, while a decrease in the incidence of hepatitis B virus by 2.5 times, hepatitis C in 2,1 times. The epidemiological and epizootic situation of natural focal and zoonanthropotic infections continues to be also complex and intensive. According to retrospective epizootic-epidemiological analysis, 14 nosological forms of infectious diseases pathogens circulate, including tularemia, leptospirosis, listeriosis, pseudotuberculosis, iersiniosis and hemorrhagic fever with kidney syndrome [3].

The problems, which were arisen in the Health Care System of the Russian Federation since the beginning of 90s, are insufficient financing by Government and shortage of medical stuff. Thereby, capacity of infectious service of Russia substantially decreased during the previous period. Provision index of infectious beds in hospitals has reduced to 52% from 1990 to 2014; provision indicator of infectious diseases' specialists decreased by 16% from 2010 to 2015. According to Russian Statistics, in 2016 the number of specialists, working at the state medical organizations, shortened in 2122 people [5]. In the Republic of Sakha (Yakutia) the number of infectious beds decreased to 30,8% from 2010 to 2017; and number of infectious diseases' specialists keeps 0.6 per 10.000 population without significant dynamics.

**Research aim** - to study contemporary state of the infectious service in the Republic of Sakha (Yakutia) based on analysis of its main indicators during the period 2000 to 2017.

#### Data and methodology of the study.

Reporting data of medical organizations and the Ministry of Health of the Republic of Sakha for 2000-2017 are applied in the analysis, as well as statistic data of demographic state and morbidity com-

pound in the Republic, statistic data of basic indicators of diseases in Russia; also, materials of case studies of infectious service issues. There was used graphical method of comparative analysis and Software of MS Excel to show line chart of data.

**Results and discussion.** In agreement with official facts, dynamics of improvement of demographic and health indicators of population from 2005 to 2013 in Russia slowed down for last three years [5]. For the last 3 years, the tendency of reducing the death rate is observed by demographic of the Republic of Sakha (Fig. 1). As reported by Russian Statistics from 2017, in the Republic the main reasons of the death were non-infectious diseases: as circulatory system illness – 44, 4%, neoplasia – 16, 8%, inner causes – 16, 1%, that correspond the mortality compound in Russia and Far Eastern Federal District. Specific gravity of the main reasons of the population's death is 77, 3%. 127 people have died by infectious and parasitic diseases, which is more than 1% of the whole number of deceased. In the Republic of Sakha (Yakutia), expected life duration grows up to 71, 68 years old on 2017 that is lower in 1.02 year than national indicators [4].

Confirming to results of 2017, in the Republic the growth of acute intestinal infections incidence is checked up adjusted etiology on 12,8%, including virus intestinal infectious on 22,9%, rotavirus infections of them on 25,6%, enterovirus infections on 12,2%, acute hepatitis in 3.8 times, whooping cough in 2.3 times, infectious mononucleosis on 34,3%, ARVI on 5%, bacterial community-acquired pneumonia on 32,9%, as well as caused by pneumococci in 2.6 times. Excess of Russian indicators of diseases in average is registered by infections as follows: enterovirus infections in 2 times, salmonellosis on 27,7%, ARVI on 31,2%, chronic virus hepatitis B in 3.6 times,

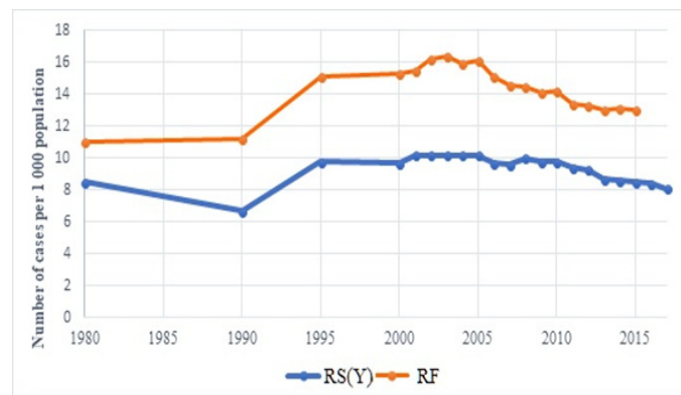
chronic virus hepatitis C in 1.5 times, careering of chronic virus hepatitis B on 32,7%, whooping cough in 2.9 times, varicella on 11,7% [3].

Total death rate from infectious diseases in the Republic of Sakha (Yakutia) has grown in 1.15 times from 2000 to 2017 and consisted 13.2 cases per 10000 population. The Figure 2 presents comparative diagram of death rate from infectious diseases in the Russian Federation, where the results in the Republic is lower in 1.5-2 times comparing with national indicators [4].

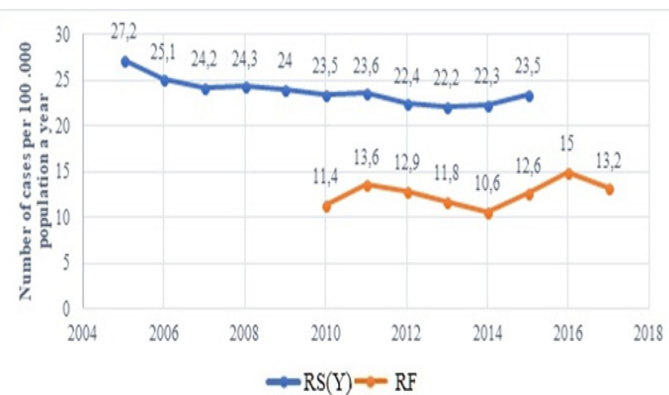
Now, constitutional and primordial incidences of infectious diseases in the Republic have tendency to constant reduction. Thus in studied period, constitutional incidence of infectious diseases decreased on 37,1%, from 4274,3 to 2685,2 per 100000 population respectively (Figure 3). Here with constitutional incidence of population in the Republic increased on 25,8% by the main classes of diseases from 2000 to 2016; 7735,0 to 10438,4 per 10000 population [4].

Organization of infectious services in the Russian Federation presented by infectious diseases rooms, infectious units of multi-field hospitals, municipal and regional infectious hospitals, some of which are the platform for the department of infectious diseases and scientific research institutes [2]. Adult infectious unit of the "Municipal Hospital" for 123 beds in Yakutsk, and 24 infectious units for 164 beds hosted by municipal and central regional hospitals introduce in-patient infectious service of the Republic. In total 390 infectious beds are in Yakutia.

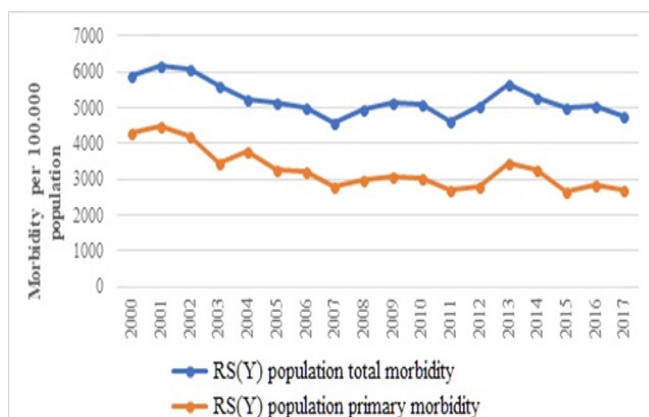
As of 2017, 65 specialists work in infectious service of the Republic of Sakha (Yakutia). They are infectious diseases' specialists of republican and administrative faculties, members of the department of the infectious diseases, phthiology and dermatovenereology of the NEFU Institute of Medicine, medical residents



**Fig.1.** Overall death rate dynamics in the Republic of Sakha (Yakutia) comparing with the Russian Federation



**Fig.2.** Dynamics of the death rate from infectious diseases in the Republic of Sakha (Yakutia) in comparison with Russian Federation



**Fig.3.** Dynamics of infectious diseases incidence in the Republic of Sakha (Yakutia)

and graduate students, from which 25 specialists (47,2%) work in Yakutsk, 29 specialists (52,7%) are in regions. Staff composition consists of 46, 4% doctors with a higher qualifying category, 16, 1% a first level and 7, 1% a second-level qualifications.

General categorization of doctors equals 69, 6%, that is explained by a large number of young specialists under 35 years old (36, 6%) in staff, the number of retirement specialists is 43, 6%. Among infectious disease specialists in the Republic, there are 12 excellent workers (17,9%) of Public Health of Yakutia, 9 excellent workers (13,4%) of Public Health of Russia, 3 candidates of Medical Science (4,5%); 2 habilitated doctors (2,9%). On the territory of the Republic 9 regions from 34 do not have infectious specialists; there are Allaikhovskiy, Abyiskiy, Anabarskiy, Eveno-Bytantaiskiy, Momsky, Ust-Mayskiy, Kobayayskiy, Zhiganskii, Namskiy regions.

There were applied comparison of sufficiency indicators of infections specialists and beds in hospitals on the dynamics of the death rate from infectious diseases. As it is shown on the Figure 4, the growth of the death rate from infectious incidence was followed by reduction of bedspace on 30,8% during the studied period.

Analogical works on the analysis of the indicators of infectious service in the Russian Federation were made by group of authors under the supervision of Academic of RAS (Russian Academy of Sciences) N. D. Yushchuk and principal of High School Organization and Management of Health Care Service G. E. Ulumbekova, where the similar results were taken. According to their analysis, unsatisfactory indicators of the death rate from some of infectious and parasitic diseases connect with steady reduction of infectious service capacity; namely low-

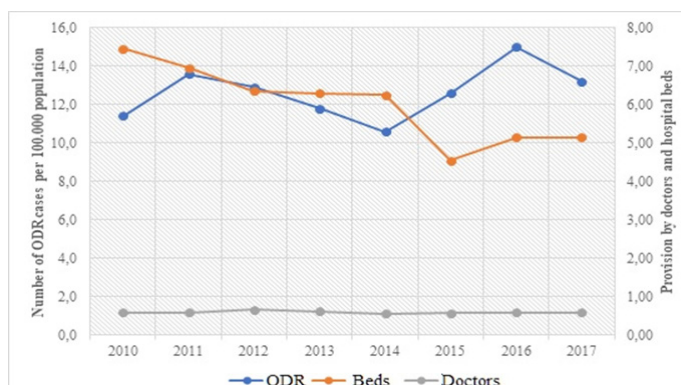
ering of the number of beds in infectious hospitals on 52% from 1990 to 2014; and decreasing of infectiologists sufficiency on 16% from 2010 to 2014. This regressive analysis shows that redundancies of infectiologists bring to one more case of the death from infectious diseases [1].

**Conclusion.** Epidemiological situation of infectious diseases in Yakutia that has developed in recent years continues to be unstable in spite of significant achievements in the Health Care System. In addition, the growth of sickness rate from 12 infectious nosology is observed in the Republic as in the Russian Federation. The death rate from infectious diseases increased in 1.15 times from 2010 to 2017 and was 13.2 cases per 100000 population. This is followed by reduction of bedspace on 30, 8%.

In view of the above, organization of medical service to infectious diseases calls for systemic actions in lowering the deficit of infectious beds and hospitals of the Republic with appropriate increase of funding in the given medical care.

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**Fig.4.** The dynamics of the overall death rate (ODR) and supply of infectious diseases' doctors and infectious beds in the Republic of Sakha (Yakutia) in the period of 2000 to 2017

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M. Yu. Rykov

## MEDICAL CARE FOR CHILDREN WITH CANCER IN THE FAR EASTERN FEDERAL DISTRICT

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### ABSTRACT

**Background.** The analysis of the quality of medical care for children with cancer is based on statistical data. Evaluation of the results is also the basis of the strategy for the development of medical care for this category of patients.

**Aim.** Analysis of the main indicators characterizing medical care for children with cancer in the Far Eastern Federal District.

**Methods.** The operative reports for 2017 of the executive authorities in the sphere of health protection of 7/9 (77,8%) subjects of the Russian Federation that are part of the Far Eastern federal districts have been analyzed (The Ministry of Health of the Republic of Sakha (Yakutia) and the Khabarovsk Territory did not provide the data).

**Results.** The number of children was 790855 (0-17 years), the number of children's oncological beds was 60 (0.7 for 10 thousand 0-17 years), the average number of days of berth employment in the year was 283.7 days. In 4 (57.1%) subjects of the department of pediatric oncology are absent, in 2 (28,6%) - there are no children's oncological beds. The number of doctors providing medical care to children with cancer is 13, of them 7 (0.8%, 0.08 for 10 thousand 0 - 17 years) have a certificate of a doctor-pediatric oncologist. In 5 (71.4%) subjects there are no doctors-children oncologists. The incidence of malignant tumors was 15 (per 100,000 0-17 years), the prevalence was 90.1 (per 100,000 0-17 years), the mortality rate was 2.9 (per 100,000 0-17 years), the one-year mortality rate - 7.6%. 5% of patients were actively detected. 52 (43.7%) of primary patients were sent to medical organizations of federal subordination, 8 (6.7%) of primary patients left the territory of the Russian Federation.

**Conclusion.** Low morbidity and mortality are attributable to defects in the account and the lack of reliable follow-up data. It is advisable to introduce electronic accounting systems. For reliable estimation of the level of provision of the population with children's cancer beds and the percentage of patients sent for treatment in medical organizations of federal subordination, audit of patients' illnesses is necessary. Deficiency of children's oncologists and a low percentage of patients identified should be eliminated by reforming the training of medical personnel.

**Keywords:** pediatric oncology, malignant tumors, morbidity, mortality, one-year mortality.

**Introduction.** The analysis of the quality of medical care for children with cancer is based on statistical data. Evaluation of the results is the basis for the development strategy of medical care for this category of patients. It is also important to coordinate the activities of regional and federal authorities aimed at increasing continuity in the provision of various stages of medical care, since pediatric oncology is a centralized area, but at the same time, the routing of patients must be dispersed throughout the country, that is, high-tech stages of treatment are conducted in medical organizations of the third B level, routine - under the conditions of the second - the third A levels [4]. For this reason, a particularly important assessment of the level of medical care in the subjects and federal districts of the Russian Federation.

**The purpose of the study** - an analysis of the main indicators characterizing medical care for children with cancer in the Far East Federal District.

**Materials and methods.** From 01.01.2017 to 31.12.2017, an environmental study was conducted in which the units of analysis were aggregated data, rather than individual individuals [5].

The operative reports of executive authorities in the sphere of health protection of 7 constituent entities of the Russian Federation that are part of the Far East-

ern Federal District are analyzed: the Kamchatka and Primorsky Territories, the Amur, Magadan and Sakhalin Regions, the Jewish Autonomous Region, the Chukotka Autonomous Okrug (Ministry of Health of the Republic of Sakha (Yakutia)) and the Khabarovsk Territory did not provide reports). The reports contained the following information: the size of the child population (0 - 17 years); number of primary patients; morbidity (by 100 thousand 0 - 17 years); the total number of children with oncological diseases on the register; the number of patients identified actively; number of deceased patients, of them among those identified in 2017; one-year mortality (%); mortality (per 100 thousand 0 - 17 years); presence in the subject of the Department of Pediatric Oncology; number of children's oncological beds; number of days of berth employment per year; number of doctors providing medical care to children with cancer, including the number of doctors who have certificates of pediatric oncologists; the number of patients referred for treatment in medical organizations of federal subordination; the number of patients who left for treatment outside the territory of the Russian Federation. Based on the obtained data, the author calculated the prevalence of malignant neoplasms (by 100 thousand 0 - 17 years), the number of children's onco-

logical beds and doctors-children's oncologists by 10 thousand 0 - 17 years, the percentage of patients hospitalized in children's oncology departments and aimed at treatment in federal medical organizations. The morbidity, mortality, and one-year mortality rates were also calculated by the author to monitor the reliability of the information contained in the reports. As the object of the study, aggregated data served: morbidity; mortality; one-year mortality; active detectability; number of doctors of children's oncologists and children's oncological beds; average number of days of berth employment per year; the percentage of patients sent for treatment in medical organizations of federal subordination and left for treatment outside the territory of the Russian Federation.

**Methods of statistical data analysis.** The sample size, which was not calculated in advance, according to the submitted reports, is as complete as possible. However, it is impossible to establish this fact precisely, since the study included all children with morphologically confirmed malignancies and reported in statistical reports. Considering the low incidence in the analyzed subjects, it is reasonable to assume that some patients were not included in the reports. This fact, as well as the absence of patients' catamnesis, do not allow to guarantee the reliability



The main indicators characterizing medical care for children with cancer in the Far East Federal District in 2017

Subjects of the Russian Federation	Indicator									
	Child population	Incidence * / prevalence*	The number of primary patients / total number of registered children	Number of patients referred for treatment to federal medical organizations (%) / who left for treatment outside the territory of the Russian Federation (%)	Number of dead patients / out of those identified in 2017	One-year mortality, %	Mortality*	The number of patients identified actively (%)	Number of pediatric oncology departments / number of children's oncological beds (**) / number of days of bed occupancy per year	Number of doctors providing medical care / of children with cancer / of them have a certificate of pediatric oncologist / % (**)
The Republic of Sakha (Yakutia)	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Kamchatka region	65432	12.3/90.8	8/59	4 (50)/1 (12.5)	2/2	25	3	2 (25)	0/5 (0.8)/285	1/n/d
Primorsky region	363902	12.9/89.3	47/324	17 (36.2)/3 (6.4)	12/2	4.3	3.3	0	1/25 (0.7)/20	6/583.3 (0.1)
Khabarovsk region	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Amur region	178297	15.2/82.6	27/147	11 (40.7)/1 (3.7)	5/2	7.4	2.8	0	0/12 (0.7)/389.8	4/250 (0.1)
Magadan region	30132	3.3/50	1/15	1 (100)/0	n/d	n/d	n/d	n/d	0/0	0/0
Sakhalin region	102250	22.5/120.6	23/123	23 (100)/3 (13)	3/2	8.7	2.9	1 (4.3)	0/8 (0.8)/440	1/0
Jewish Autonomous Region	37597	16.2/89.2	6/33	0/0	1/1	16.7	2.7	0	0/0	0/0
Chukotka Autonomous District	13245	53.8/84.6	7/11	6 (85.7)/0	0	0	0	4 (57.1)	0/10 (7.6)/n/d	1/0
Total	790855	15/90.1	119/712	52 (43.7)/8 (6.7)	23/9	7.6	2.9	6 (5)	1/60 (0.7)/283.7	13/760.8 (0.08)

Note: \* - per 100 thousand children population aged 0–17 years. \*\* - per 10 thousand children population aged 0–17 years. n/d - no data

of data on morbidity, mortality and one-year mortality.

The statistical processing of the material was carried out on a personal computer using the program STATISTICA v. 7.0 (StatSoft Inc., USA). For the value of statistical significance, the value  $p < 0.05$  was assumed. An estimate of the reliability of the relative frequency difference was carried out by the Student's test.

**Results.** The main indicators characterizing medical care for children with cancer in the subjects that make up the Far Eastern Federal District are presented in Table.

The number of children's population was 790855 people (0 - 17 years). The maximum number of children was recorded in the Primorsky Territory (363902 people), the minimum in the Chukotka Autonomous Okrug (13245 people).

There was 1 children's oncology department (Primorsky Krai). In 4 (57.1%) subjects of the department of pediatric oncology are absent: medical care for children with cancer falls on beds allocated in other departments of multidisciplinary children's clinical hospitals.

The number of children's oncological beds was 60 (0.7 per 10 thousand 0 - 17 years). In 2 (28.6%) subjects (Magadan Oblast and the Jewish Autonomous Region) there are no children's oncological beds. The smallest number of beds was noted in Primorsky Krai and the Amur Region (0.7 per 10,000 0-17 years), the largest in the Chukotka Autonomous District (7.6 per 10,000 0-17 years).

The average number of days of berth employment in the year was 283.7 bed days. The largest number of days of berth employment in the year was noted in the Amur Region (389.8), the smallest - in the Primorsky Territory (20).

The number of doctors providing medical care to children with cancer was 13, of which 70 (60.8%, 0.08 for 10 thousand 0 - 17 years) are certified as a pediatric oncologist. In 4 (57.1%) subjects (Magadan and Sakhalin regions, the Jewish Autonomous Region, the Chukotka Autonomous Okrug) there are no doctors-children oncologists and children's oncological beds. The number of

doctors-children's oncologists is the same - 0.1 per 10 thousand children's population 0-17 years.

The number of primary patients with malignant tumors was 119, on dispensary registration (who had reached remission and continuing treatment) - 712. Thus, the incidence rate in the Far Eastern Federal District in 2017 was 15, the prevalence was 90.1 100 thousand children (0 - 17 years).

The highest incidence was registered in the Chukotka Autonomous District (53.8 per 100,000 0-17 years), the lowest in the Magadan Region (3.3 per 100,000 0-17 years), the highest prevalence in the Sakhalin Oblast (120.6 for 100 thousand 0 - 17 years) the lowest - in the Amur region (82.6 per 100 thousand 0 - 17 years) (Fig. 22, 23). The number of deceased patients in the FEFD was 23, of them among the identified in 2017 - 9. Thus, the death rate was 2.9 per 100 thousand 0 - 17 years, a one-year mortality rate of 7.6%. The highest mortality was registered in the Primorsky Territory (3.3 per 100,000 0-17 years), the lowest in the Jewish Autonomous Region (2.7 per 100,000 0-17 years) (Figure 22). The largest one-year mortality was recorded in the Kamchatka Territory (25%), in the Chukotka Autonomous District it was 0%.

The number of patients detected actively was 6 (5%). In a number of subjects (Primorsky Krai, Amur Oblast, Jewish Autonomous Region), during planned preventive examinations of the child population of malignant neoplasms, there was no evidence. The maximum percentage of patients identified actively was registered in the Chukotka Autonomous District (57.1%).

52 (43.7%) patients were sent to medical organizations for federal subordination. The highest index was registered in the Magadan and Sakhalin regions (100%), the lowest in the Primorsky Territory (36.2%).

For treatment outside the territory of the Russian Federation, 8 (6.7%) of primary patients left.

**Discussion.** Operative reports 5 (71.4%) of the subjects contained 6 errors in the calculation of some indicators.

In the reports of the Kamchatka and Primorsky Krai, the Amur Region and the Jewish Autonomous Region, the figures for a one-year mortality are not true: 9.1%, 1.86%, 3.17%, 100% with true values of 25%, 4.3%, 7, 4%, 16.7%, respectively. Also in the reports of the Jewish Autonomous Region and the Chukotka Autonomous Okrug, incidence rates were erroneously calculated: 15.9 and 52.9, with true values of 16.2 and 53.8 per 100,000 population 0-17 years, respectively.

Some reports do not contain information in full: The Kamchatka Krai did not provide data on the number of doctors who have a certificate of a pediatric oncologist, Magadan Oblast did not provide data on the number of deaths, one-year mortality, mortality and active detectability, the Chukotka Autonomous District did not provide data on average number of days of employment of a berth in a year.

The time characteristics in the reports (the average time taken to establish the diagnosis, the average time elapsed from the moment of verification of the diagnosis to the start of treatment, and the average time spent on diagnosing patients who died of malignant neoplasms of patients) are untrue, since it is highly doubtful that the average The quantities calculated, as is known, by adding the numbers and dividing the obtained number by the number of terms, can be integers, whereas in most of the reports comrade values are 7, 1 and 7, respectively. It is obvious that in some cases the morphological verification of the diagnosis takes up to 14 days. In the Far East Federal District, the "leader" in terms of the incidence rate in 2013 - the Sakhalin region - has maintained a high incidence rate (18.5 and 22.5 per 100,000 0-17 years, respectively), but is in second place behind Chukotka Autonomous District (53.8 per 100 thousand 0 - 17 years), the incidence of which is the highest among all subjects of the Russian Federation. At the same time, the largest number of children's oncological beds in the Chukotka Autonomous Okrug is 7.6 per 10,000 0-17 years, but not a single pediatric oncologist.

Morbidity in the Jewish Autonomous Region, which in 2013 was minimal in the Far East Federal District, increased significantly (2013 - 8.1, 2017 - 16.2). In 2017, the lowest incidence in the federal district was registered in the Magadan Region - 3.3 per 100 thousand 0 - 17 years [2]. This indicates that the detectability and accounting for the past 5 years in some entities have increased. Although the incidence in the analyzed federal district is significantly lower than

in the US and Europe, but higher than in countries with low reliability of statistical data, for example, in the Central Asian Republics (Kyrgyzstan, Uzbekistan, Tajikistan) [1, 7].

The provision of the population with pediatric oncological beds has slightly increased (2013 - 0.53, 2017 - 0.7 per 10 thousand 0 - 17 years) [3].

The provision of the population by doctors-pediatric oncologists decreased from 0.11 to 0.08. It, obviously, is due to the fact that in 2017 the number of doctors with certificates of children's oncology was indicated in the reports [2].

The percentage of patients sent for treatment in medical organizations of federal subordination decreased from 75.3 to 43.7%. It is quite difficult to assess this indicator, since pediatric oncology is a centralized field of medicine and patients should receive many stages of treatment on the basis of federal medical organizations. For this reason, the actual value seems to be quite low. Although this is only a subjective assessment and it requires an audit of patients' illness histories [2].

It is not possible to compare prevalence, mortality, one-year mortality, active detectability, the average number of days of occupancy of a child cancer cage in a year, and the percentage of patients leaving for treatment outside the Russian Federation, since in 2013 the reports did not contain this information.

The average number of days of berth employment per year is at an extremely low level-283.7 bed days, respectively.

In some subjects, this indicator is at an extremely low level. For example, in the Primorsky Territory - 20 bed days, in the Kamchatka Territory - 285 bed days. This indicates that in these subjects there is an excess of pediatric oncological beds that are not filled. In some subjects, this indicator is at an extremely high level and exceeds 365 hospital days. For example, the Amur region - 398.8 bed days, the Sakhalin region - 440 days. Obviously, in these subjects, several patients are hospitalized for children's oncological beds at the same time, which indicates the inadequacy of children's oncological beds in these subjects.

In order to eliminate the identified data defects and the reasons leading to the appearance of such data, it is necessary to expand informatization, to introduce an electronic database of children with oncological diseases, which will eliminate the "subjective" factor both in the preparation of reports and during the choice of treat-

ment tactics and patient routing [3, 5].

Although the reports were signed by the heads (deputy heads) of the executive bodies in the sphere of health protection of the subjects of the Russian Federation, most of the data were provided by the main freelance pediatric specialists oncologists, which does not exclude the subjective factor, and as a result, mistakes in completing the questionnaires that were have been identified.

From conversations with some compilers, it was found that some of them did not know how to calculate the levels of morbidity, mortality and one-year mortality, while others cited a lack of time for the correct filling in questionnaires. Another reason for respondents was the lack of reliable statistics (the number of primary patients, the total number of children registered, etc.).

**Conclusion.** The incidence rates in the RF subjects of the FEFD are significantly lower than those in Europe and the United States, but higher than in countries with low statistical reliability. This indicates the remaining defects of detectability. But there is a positive trend. The mortality rate is at an acceptable level, which may be due to the lack of reliable follow-up data. The percentage of patients identified actively, it is necessary to increase, including by the wide introduction in the clinical practice of the algorithm for referring the patient to a consultation with a pediatric oncologist. For a reliable assessment of the level of provision of the population with children's cancer beds, audit of patient records is necessary.

**Conflict of interest.** The author of the article confirmed the absence of a conflict of interests, which must be reported.

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## ACTUAL TOPIC

S.S. Sosina, J.V. Vinokurova, E.P. Yakovleva, I.N. Nikolayeva, A.P. Sleptsov

## THE DETECTABILITY OF HELICOBACTER PYLORI CAGA STRAIN IN ADULTS AND CHILDREN ACCORDING TO THE DATA OF RH№1-NCM

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### ABSTRACT

The Republic of Sakha (Yakutia) belongs to Arctic territories. Hard social and economic conditions cause broad development of helicobacter infection in the republic. A comparative analysis of detectability of *Helicobacter pylori* CagA strain among adults and children with chronic gastritis since 2012 to 2016 according to Republic hospital №1 - National center of medicine (RH №1-NCM) revealed a distinct decrease in these indexes among adults and children with chronic gastritis. Thus it demands its further identification and treatment for prevention of stomach diseases of oncological risk group. This article presents research data of detectability of *Helicobacter pylori* among adults and children for 6 years in RH №1-NCM clinical-immunological laboratory by method of enzyme immunoassay on antibodies to antigen Cag A *Helicobacter pylori*. The blood serum of patients from the National center of medicine was the material for this research.

15868 patients were examined, 6993 of them were revealed *Helicobacter pylori* Cag A that made 44,1%. The detectability for the research period decreased from 49,6% to 40%. 3827 adults out of 8272 patients were revealed Hp (+) Cag A that made 46,3%, and detectability decreased from 52% to 42% for this period. Among 7596 sick children a decrease in detectability of Hp (+)CagA was from 47,4% to 39,1%. Thus, a comparative analysis of detectability of Hp (+)CagA for the reporting period proved a distinct decrease in indexes among adults and children with chronic gastritis.

Serological diagnostic methods for diagnosing the pathology of the upper digestive tract are of great importance for mass medical examinations. They allow diagnosing the disease in the early (asymptomatic) stage.

There is a tendency to reduce the rates of *Helicobacter pylori* infection among patients with chronic gastritis, which requires further identification, treatment and prevention among the population.

**Keywords:** Far North, Republic of Sakha (Yakutia), *Helicobacter pylori*, Cag A antigen, clinical and immunological laboratory, RB N1-NCM (Yakutsk), screening, diagnosis, immunoassay, antibodies to Cag A *Helicobacter pylori* antigen, treatment.

**Introduction.** In most cases, *Helicobacter pylori* infection which is always associated with gastritis is the cause of atrophic gastritis. Almost 50% of the patients infected with *Helicobacter pylori* develop atrophic gastritis which in most cases leads to stomach carcinoma and

90% of cases is the cause of peptic ulcer [1].

According to researches, chronic gastritis among indigenous people of Yakutia is characterized by the considerable specific gravity of atrophic gastritis (38,5-57,1) with a larger frequency of atrophic

antral forms of gastritis at young age.

According to researchers of the Yakut scientific center, Russian Academy of Medical Science of the Republic of Sakha (Yakutia), *Helicobacter pylori* infection among adult population of Yakutia was 76,1% [2]. In the common structure of the



examined children and teenagers *Helicobacter pylori* infection was 58,5% [3]. Atrophic gastritis were at 8,5% of teenagers and 34% of adults among indigenous people of the North. It was combined with intestinal metaplasia, stomach mucosa dysplasia. Authors emphasize HP infection value in the development of stomach mucous restructuring. A distinct correlative connection between HP infection and precancerous state was established: atrophy, dysplasia, intestinal metaplasia of stomach mucous at patients with HP gastritis.

According to Kurilovich S.A., Reshetnikov O.V. atrophy frequency in a stomach body at the population of Novosibirsk, urban and country people of Yakutia was respectively 10,1, 16,7 and 25,6%, and in antral department – 10,7, 25,6 and 8,9%. “GastroPanel” was used [4]. The total atrophy was registered in 1% in all groups. *Helicobacter pylori* infection was revealed at 78 – 88%.

Nowadays the question of differentiation of various strains of *H.pylori* on the basis of their heterogeneity on virulence factors is being studied.

#### Materials and research methods.

We revealed a *helicobacter* infection at various diseases of inner organs of patients by noninvasive respiratory method – “Helic-test”. The analysis of 748 protocols of clinical trial, esophagogastroduodenoscopy and “Helic-test” at adults and children in RH №1-NCM (306 adult patients (137 males and 169 females from 19 to 79 years old) and 442 children (239 girls and 203 boys, aged from 1 year to 18 years) was carried out.

We made a comparative analysis of detectability of HP infection indexes among patients with chronic gastritis for the last 5 years by Republic hospital №1 data, Yakutsk. The research on detectability of *Helicobacter pylori* among adults and children since 2012 to 2016 was done on the basis of Republic hospital №1 clinical-immunological laboratory by EIA method on antibodies to antigen CagA *Helicobacter pylori*.

**Results and discussion.** *Helicobacter pylori* was revealed at 74% out of 270 adults patients (males - 72%, females - 76%). 79% of cases were HP (+) among 164 patients with chronic gastritis. 67% were HP at 24 patients with peptic ulcer of stomach and duodenum. In 28 cases chronic gastritis was combined with

**Detectability of *Helicobacter pylori* among adults and children for the period from 2012 to 2017 years**

Year	Total	Hp(+)/%	Total adults	Hp(+)/%	Всего детей Total children	Hp(+)/%
2012	2996	1487/49.6	1434	747/52	1562	740/47.4
2013	2722	1233/45.3	1317	620/47	1405	613/43.6
2014	2482	1166/47	1290	647/50.2	1192	519/43.5
2015	2555	1041/40.7	1569	680/43.3	986	361/36.6
2016	2635	1050/40	1376	580/42	1259	470/37.3
2017	2478	1016/41	1286	553/43	1192	466/39.1
Mean %	15868	6993/44.1	8272	3827/46.3	7596	3169/41.7

GERD, and HP (+) was in 61 cases.

According to the detectability of *Helicobacter pylori* among adults and children since 2012 to 2017 it turned out that 6993 out of 15868 were revealed *Helicobacter pylori* Cag A that made 44,1%. The detectability for the research period decreased from 49,6% to 41%. 3827 adults out of 8272 patients were revealed Hp(+) CagA that made 46,3%, and detectability decreased from 52% to 43% for this period. Among 7596 sick children a decrease in detectability of Hp(+) CagA was from 47,4% to 41,7%. Thus, a comparative analysis of detectability of Hp(+)CagA for the reporting period proved a distinct decrease in indexes among adults and children with chronic gastritis.

**Conclusion.** Serological diagnostic methods for diagnosing the pathology of the upper digestive tract are of great importance for mass medical examinations. They allow to diagnose the disease in the early (asymptomatic) stage.

There is a tendency to reduce the rates of *Helicobacter pylori* infection among patients with chronic gastritis, which requires further identification, treatment and prevention among the population.

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## MEDICAL AND SOCIAL ASSISTANCE TO HIV-INFECTED PATIENTS

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### ABSTRACT

The purpose of research is to study the quality of medical and social care and the attitude of the population towards HIV-infected people in Yakutsk in the Republic of Sakha (Yakutia). The main methods of research are the analysis of normative and legal acts and statistical data, a sociological questioning. A study of the opinion of HIV-positive people about their satisfaction with the quality of medical and social services, living standards and social status showed that 90% of patients receive the necessary medical care and often attend the AIDS Center.

The results of the research showed that the majority of HIV-infected people in Yakutsk, young people aged 19 to 29, contracted sexual intercourse, which in turn indicates that there are still many young people who are poorly informed about the threat HIV infection and other STDs. Survey of HIV-infected and medical workers of the State Bank of the Yakut Republican Center for AIDS Prevention and Control revealed that in our republic a sufficiently effective and qualified medical and social work is carried out, providing crucial help to HIV-infected people, but not enough social assistance is provided.

It has been found that the society is generally benevolent towards HIV - infected patients and is ready to provide some form of support to a person living with HIV, regardless of whether they know him or not. However, the responses also showed that HIV-positive status appears as an extremely strong social label, significantly worsening the attitudes of others around it. It was noted the need to open a sanatorium-type rehabilitation center for HIV-infected people.

**Keywords:** HIV - infected, medical and social services, medical aid, psychological help.

**Introduction.** In the modern world, a serious danger to life and health of people is represented by diseases denoted by the term "socially dangerous diseases". In the Russian Federation, diseases approved by Government Decree No. 715 of 1 December 2004 on the approval of the list of socially significant diseases and a list of diseases that pose a danger to others are considered socially dangerous diseases. The resolution lists the following diseases: HIV, viral fever, hepatitis B, hepatitis C, sexually transmitted infections, tuberculosis, cholera, and others [1]. In the Republic of Sakha (Yakutia), the most dangerous and widespread, difficult to cure or completely incurable, are the diseases of the human immunodeficiency virus, tuberculosis and hepatitis B and C.

HIV is a slowly progressing disease caused by the human immunodeficiency virus. The virus affects the cells of the immune system. As a result, the work of the immune system is inhibited, the syndrome of acquired immune deficiency (AIDS) develops, the patient's body loses the ability to protect itself from infections and tumors, secondary opportunistic diseases that are not characteristic of people with normal immune status. AIDS, in turn, is the terminal stage of HIV infection, the period from infection with the human immunodeficiency virus to the development of AIDS lasts an average of 9 to 11 years.

The main normative legal act regulating the provision of medical and social assistance to persons affected by HIV in the Russian Federation is the Federal Law of 30 March 1995 on the prevention

of the spread of the disease caused by the human immunodeficiency virus (HIV infection). «In addition to this law, at the present stage, the organization of medical and social care for people with HIV and AIDS is implemented in accordance with the Fundamentals of the Russian Federation legislation on the protection of public health and Federal Law No. 38-FZ of 30 March 1995 "On preventing the spread of the disease in the Russian Federation, caused by the human immunodeficiency virus (HIV infection) ".

Thus, medico-social work with HIV-infected and AIDS patients is based on the legal framework that determines the social status, rights and duties of this contingent. Expansion of the list of normative legal acts and clarification of their content is associated with an increase in the number of the disease, as well as awareness of the need to provide social and medical assistance to HIV-infected and AIDS patients.

According to the statistics of 2016, all HIV cases in the Republic of Sakha (Yakutia) are 1752, of which 1332 Russian citizens, including 833 men and 489 women, the remaining 420 patients are migrants from other countries. In the first place in terms of the number of HIV infected is Mirninsky district - 495, then the city of Yakutsk - 467 and in third place Neryungri district - 207. The greatest proportion of HIV-infected falls on the age of 19-29 years-55.1%. It should be noted that analysis of HIV-positive statistics shows that the number of people infected with this virus is growing rapidly in the Republic of Sakha (Yakutia) and throughout the Russian Federation.

The **purpose** of our study is to study the quality of medical and social care and the attitude of the population towards HIV-infected people in Yakutsk in the Republic of Sakha (Yakutia). The main methods of research are the analysis of normative and legal acts and statistical data, a sociological survey.

A study of the opinion of HIV-positive people about their satisfaction with the quality of medical and social services, living standards and social status showed that 90% of patients receive the necessary medical care and often attend the AIDS Center. Half of the respondents believe that they receive social assistance, 30% of the subjects found it difficult to answer this question, 20% of the patients answered negatively. Patients have a fairly complete picture of the consequences of AIDS and 80% of them believe that it is incurable. Half of the patients do not hide their positive diagnosis of HIV infection from their relatives, friends and close people, receive moral support and discuss with them problems related to the disease.

To the question "What kind of help would you like to receive from the public?" many refrained from answering, some answered: "Understandings" and "Calm attitude towards HIV-positive people". Naturally, people are different, and react differently to the fact that their close person, relative, friend, friend is suffering from HIV and because of insufficient information about the illness, and possibly lack of psychological preparedness, they may get scared and turn away from the latter.

Nevertheless, 70% of the polled pa-

tients noted that they do not feel a sense of discrimination by the society.

Half of the respondents are satisfied with the help provided by the state, the patients additionally suggested that they would like to receive assistance in the form of cash payments. It was also noted the desire of patients to establish a sanatorium-type rehabilitation center for HIV-infected people. Perhaps opening such a facility would help many people living with HIV raise their spirits, help them to intensify their internal forces to prolong their lives.

Based on the results of the study, it can be concluded that a larger number of people suffering from HIV in Yakutsk, namely 80% have sexually transmitted infections, which indicates that there are still a lot of people who do not adhere to safe sex and lead a lascivious lifestyle. Perhaps this is due to the lack of public awareness about the threat of HIV infection and irresponsible treatment of their health by individuals.

As the study showed, in general, people are exposed to HIV at a young age - from 17 to 25 years. This indicator is confirmed by the data of the statistical department of the AIDS Center, according to which 60% of patients are under 30 years old.

The next stage of our study was a survey of medical personnel of the State Budgetary Agency of the Republic of Sakha (Yakutia) "Yakut Republican Center for AIDS Prevention and Control" to identify and assess the quality of medical and social services for HIV-infected people in the Republic of Sakha (Yakutia).

GBU "Yakut Republican Center for AIDS Prevention and Control" as a multidisciplinary medical and prophylactic institution conducts, mainly, medical, diagnostic and medico-preventive work, which was confirmed by the conducted research.

In the survey, 5 doctors from the AIDS center clinic, 4 nurses and 1 psychologist who were directly involved with HIV-infected patients participated.

An analysis of the responses of the survey participants showed that the main activity of the AIDS Center is the provision of medical care (56% of responses) to infected patients, followed by psychological support (25%) and social (13%). Legal assistance is not rendered at all, which, in principle, does not fall under the responsibility of this institution.

AIDS Center's medical professionals, as specialists who most often contact people with HIV-positive status, are sure

that HIV-infected people have a greater sense of rejection and loneliness, which in turn is more likely due to the attitude of society towards their diagnosis. Employees of the AIDS Center, as professionals in their case on HIV in our country, believe that people most affected by HIV are lacking effective social assistance from the state, as well as subsequent rehabilitation work.

According to the medical staff of this institution, HIV-positive people badly need psychological help, which is included in the complex of the concept of "medical and social assistance", and equally need social assistance, intensive treatment and support of the community.

The degree of rendering medical care to HIV-infected people in the Republic of Sakha (Yakutia) "by the AIDS Center staff is not very high - an average of 7.1 points out of 10, and medical and social assistance by 6 points.

The results of the research also revealed personal qualities of employees, such as tolerance, compassion and goodwill. Doctors, nurses and a psychologist of this institution in the process of communicating with their patients gently learn to "live with a diagnosis", "adhere to an optimistic attitude", "observe a healthy lifestyle", "trust doctors" and "do not give up".

Summarizing the above, it can be concluded that HIV-infected patients could learn to live with this status. Overcoming the attendant difficulties, as well as maintaining the old way of life are possible with timely psychological support and comprehensive rehabilitation work.

One of the tasks of our study was to study the attitude of Yakutsk residents to HIV-infected people. A total of 53 women, 47 men, were interviewed with different members of the community: 25 school-children, 25 students, 25 workers and 25 pensioners.

An analysis of the answers of the subjects found that the majority of respondents (66%) feel compassion and pity for HIV-infected people, and also revealed that the society is ready to provide some form of support for a person living with HIV, regardless of whether they are he knows them or not. Many subjects (62%) noted that they would not turn away from a relative or someone with strong connections if the latter were found to have HIV-positive status, but would support them. 74% of respondents are ready to provide moral support and help in the fight against the virus, and 19% could help financially and only 4% did not an-

swer. 96% of the interviewed people noted that they could provide some form of help to HIV-infected people, perhaps such a positive attitude of almost all respondents is due to the fact that there were no such items as "would not help" in the answers. 4% chose the answer "other" without specifying the reason. 47% of respondents would advise intensive treatment, 33% - not to give up and fight for life, 15% - to live a normal life and not "fixate" on the problem, 2% - turn to a psychologist and 2% - refrain from advice. All the advice was benevolent, no one showed a negative attitude, which indicates that there is no discrimination against HIV-infected people.

However, when questions relate to close, contact with HIV-infected individuals, the answers become less comprehensible and compassionate. So, to the question "What would you do if you learned that your child goes to a kindergarten or to a school where a child with HIV is living?", Some gave negative answers until the child was excluded from the institution of an HIV-infected child (10%). Also, there are answers that are close in meaning to the previous one (5%) - they would arrange a scandal. 20% of the subjects would transfer their child to another group or class, 38% would transfer to another institution. 9% refrained from responding, and only 17% did not take any action. These results also indirectly show that there is a label placed on people living with HIV. Respondents' answers indicate that HIV-positive status is an extremely strong social label that makes a person "not desirable" a member of society, thereby significantly worsening the attitude towards him.

**Conclusion.** HIV infection affects all major aspects of the life of an infected person. The severity of the patient's condition is due not only to physical causes. Feelings, thoughts, experiences of people living with HIV, their changed social status, relationships with others are no less important for their future life than the presence or absence of clinical symptoms of the disease. Adaptation of HIV-infected people to the changed conditions of life depends on many factors, first of all on the timely provided psychological support, which is indicated in their answers by patients and AIDS doctors of the Yakutsk Center.

It is known, although at the moment this disease is not yet curable, the successes of rapidly developing antiretroviral therapy give hope to these patients. Currently, the life expectancy of an HIV-



infected person with active participation of a patient in the treatment process can be equal to the life expectancy of an average healthy person. HIV-infected patients could learn to live with this status [1]. Overcoming the psychological and social difficulties that have arisen, as well as the restoration and preservation of the old way of life are possible with timely psychological support and comprehensive rehabilitation work. That is why the problem of social rehabilitation is relevant.

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# MOLECULAR GENETIC STUDIES AS AN AUXILIARY METHOD FOR DETERMINING RISK FACTORS IN THE CLINICAL EXAMINATION OF THE ADULT POPULATION

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## ABSTRACT

Indicators of morbidity of adult population according to out-patient office of Hospital of the Yakut Science Center of Complex Medical Problems (Yakutsk) during 2015-2017 are presented in article. The characteristic of dynamics and structure of cases of the general and primary incidence is given. Decrease in level of the general incidence for all analyzed period is established. In structure of the general incidence of adult population the prevalence of diseases of respiratory organs and the blood circulatory system is revealed. The analysis of dynamics of indicators of primary incidence has shown the stable growth of her level with prevalence a case of diseases of respiratory organs.

The obtained data on the dynamics and distribution patterns of diseases have served as the basis for selecting the directions of molecular genetic research, the search for associations of genetic markers of the system of cytokines responsible for the development and maintenance in the body of chronic systemic inflammation, the genes B2 - adrenoreceptor and genes of cold receptors involved in the hereditary predisposition to hyperreactivity of the respiratory and the cardiovascular system in response to the effects of low temperatures.

**Keywords:** clinical examination, morbidity general and primary, structure and dynamics of morbidity, genes of cytokines, adrenoreceptor genes, cold receptor genes.

**Introduction.** Clinical examination is a method of systematic medical observation of the health status of certain groups of the healthy population or patients with chronic diseases with the aim of preventing and early detection of diseases, timely treatment and prevention of exacerbations.

Clinical examination is aimed primarily at the early detection of chronic non-infectious diseases, which include: diseases of the circulatory system and especially ischemic heart disease and cerebrovascular diseases, malignant neoplasms, diabetes, chronic lung diseases, diseases of the musculoskeletal system, gastrointestinal tract and urinary system. These diseases cause more than 75% of all mortality in our country.

In addition, according to the regulatory

documents, a clinical examination is designed to identify and correct the main risk factors for the development of diseases, such as elevated blood pressure, cholesterol and glucose in the blood, smoking, harmful alcohol consumption, overweight or obesity [3]. But, taking into account that even minimal deviations from the norm of laboratory or functional indicators, and even more so the initial clinical manifestations of diseases occur when there are already established pathological processes in the human body, the question arises of the timeliness of clinical examinations regarding the prevention of risk factors.

To improve the effectiveness of measures to identify predisposing risk factors, modern medicine has technologies that are able to calculate the

risk of developing diseases long before the first clinical, laboratory and functional changes appear, in other words using high-tech diagnostic methods, it is possible to carry out not only accurate molecular diagnostics, but also to determine a person's predisposition to a particular disease [2].

The use of the results of molecular genetic testing can significantly facilitate the solution of the task of conducting all citizens with a history of risk factors for brief preventive counseling, as well as for individuals with high and very high total risk of individual in-depth and group (patient's school) preventive counseling in the context of dispensarization. Such active prophylactic interventions make it possible to quickly and significantly reduce the likelihood of the development

of dangerous chronic non-infectious diseases in each particular person, and in those already suffering from such diseases significantly reduce the severity of the course of the disease and the incidence of complications [3, 4].

The introduction of active medical examinations using the capabilities of molecular genetic methods will enhance the effectiveness of preventive measures to reduce mortality and disability of the population, reduce economic losses, by restoring labor potential.

For an informed choice and correction of the directions of molecular genetic studies to determine biological predictors of susceptibility, in order to optimize measures for the organization of preventive measures, an analysis of the indicators of the clinical examination of the outpatient department of the Hospital YSC CMP was carried out.

**Materials and methods.** To assess the organization of the dispensarization carried out, we used the method of analyzing the indicators of the clinical examination of adults aged 18 to 80 years based on the statistical reports of the outpatient department of the Hospital of the Nuclear Physics Center for the period 2015-2017.

All participants of the clinic were examined by a therapist and narrow specialists: a neuropathologist, obstetrician gynecologist, surgeon, oculist.

Laboratory and functional studies were performed: clinical blood analysis, urinalysis, biochemical blood analysis (cholesterol, sugar, total protein, creatinine, fibrinogen, bilirubin, AST, ALT, sodium, potassium), blood test for tumor marker PSA (for men older 51 years old); fecal occult blood; cytological examination of a smear from the cervical canal; electrocardiography (ECG); fluorography (FLG), mammography (for women over 39 years old). Statistical data processing was carried out using descriptive statistics methods [1].

**Results and discussion.** According to the results of the analysis, for 3 years, 2348 people were subject to planned medical examination. In 2015, dispensarization was carried out in relation to - 657 people, in 2016 - 789 people, in 2017 - 874 people, thus, for the period from 2015 to 2017. 2320 people underwent medical examination, or 98.8% of the planned volume.

According to the results of research and examinations of medical specialists, each patient was determined by the health group: Group 1 - the patient is healthy; Group 2 - the patient is healthy, but has

risk factors (smoking, increased weight, elevated blood cholesterol, etc.); Group 3 - a patient who needs to be examined or treated in a polyclinic; 4 patient group who needs inpatient treatment; 5 patient group needs a high-tech type of medical care.

Indicators of the distribution of the attached population are presented in table 1. According to the results of clinical, laboratory and instrumental examination, the largest number of people were identified in the 3rd group of health, and amounted to 53.9 - 85% of the total number of those undergoing medical examination. The analysis of the dynamics of population distribution indicators by groups showed an annual increase in the number of population assigned to groups 1 or 2 of health, which indicates the timely prevention and diagnosis of diseases.

Table 2 presents the dynamics of the level of general morbidity of the attached population. General morbidity is the totality of all the diseases among the population, both newly diagnosed in a given calendar year and registered in previous years, about which patients again applied in a given year. Analysis of the dynamics of indicators of general morbidity showed a certain increase in its level in 2017 compared to the level of 2016, which is explained by the increase in the number of attached population of the older age group in this period. However, the overall incidence rate for the entire analyzed period decreased by 1.3 times, which is the result of timely preventive work aimed at early detection and treatment of diseases.

An analysis of the overall morbidity structure according to the data of the outpatient department showed that diseases of the respiratory system and circulatory system are in the lead among adult diseases, which may be due both to the high level of this pathology among the population and to the diagnostic capabilities and active identification of patients with these diseases. organs and systems (table 3).

The analysis of the dynamics of the indicators of primary morbidity is presented in table 4. Primary morbidity

characterizes the totality of new, nowhere previously recorded, and for the first time in a given calendar year, diseases detected per 1,000 people and registered among the population. The analysis of the dynamics of the indicators of primary morbidity showed a steady growth of its level, with the maximum rates in 2016, which is explained by the increase in the number of the attached population of the older age group during this period, as well as the active detection of diseases in the newly attached population. It should be noted that the primary incidence rates of 2017 with the same size of the attached population decreased compared with the previous figures of 2015 -16, which may indicate a systematic and effective medical examination, as well as the organization of preventive measures aimed at reducing the incidence of whole.

Analysis of the structure of the primary morbidity for the entire analyzed period revealed the following features, first place in frequency is occupied by respiratory diseases, second - diseases of the genitourinary system, third place - diseases of the circulatory organs (table 5). The maximum increase in the rates of newly diagnosed diseases of the urogenital system and circulatory system is in 2016, which may be associated with an increase in the number of assigned population and the active detectability of these diseases. Despite the fact that respiratory diseases occupy a leading place throughout the analyzed period, in general, they tend to decline.

**Conclusion.** Thus, an analysis of the organization of the outpatient dispensation of the attached population of the Hospital of the YSC CMP has shown that the systematic implementation of preventive measures helps to reduce the incidence rate in general.

Table 1

Population distribution by health groups for 2015 - 2017

Period (year)	Health group			Patients from the 3rd group, transferred to groups 4 and 5	
	1 group n. (%)	2 group n. (%)	3 group n. (%)	4 group n. (%)	5 group n. (%)
2015				25 (4.5)	7 (1.3)
2016	175 (22.1)	189 (24)	425 (53.9)	19 (4.5)	8 (1.9)
2017	115 (13.2)	123 (14.1)	636 (72.7)	17 (2.7)	21 (3.3)

Table 2

The general incidence for the years 2015 - 2017

	2015	2016	2017
Absolute figure	15 971	10 914	12 060
Per 1000 population	1651,6	1091,4	1246,9

The obtained data on the dynamics and structure of the distribution of diseases served as the basis for choosing the directions of molecular genetic studies, the results of which will be used as an additional factor in planning personalized prevention and treatment programs, taking into account the genetic characteristics of patients.

Currently, the staff of the laboratory of population genetics and hereditary pathology of the YSC CMP within the framework of the research «Study of the genetic structure and load of the hereditary pathology of populations of the Republic of Sakha (Yakutia)» are conducting research on the formation of bronchopulmonary and cardiovascular pathologies prevalent in patients according to dispensary data. An association of genetic markers of the cytokine system responsible for the development and maintenance of chronic systemic inflammation, adrenoblocker genes and cold receptor genes involved in hereditary susceptibility to hyperreactivity of the respiratory and cardiovascular systems in response to the effects of low temperatures.

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Table 3			
The rating of registered diseases for 2015 – 2017, %			
	2015	2016	2017
1 place	Diseases of the cardiovascular system (17,6)	Diseases respiratory organs (19,4)	Diseases respiratory organs (19,6)
2 place	Diseases respiratory organs (14,6)	Diseases of the cardiovascular system (15,7)	Diseases of the cardiovascular system (18,0)
3 place	Diseases of the urogenital system (11,3)	Diseases of the urogenital system (13,4)	Diseases of the urogenital system (12,9)

Table 4			
Indicators of primary morbidity for 2015 - 2017			
	2015	2016	2017
Absolute figure	3197	5603	4490
Per 1000 people	303,6	579,4	464,3

Table 5			
The rating of newly diagnosed diseases for 2015-2017			
Год	2015 abs.(%)	2016 abs.(%)	2017 abs.(%)
1 place	Diseases respiratory organs 1589 (49,7)	Diseases respiratory organs 1533 (27,3)	Diseases respiratory organs 1481 (33)
2 place	Diseases of the genitourinary system 310 (9,7)	Diseases of the genitourinary system 927 (16,4)	Diseases of the genitourinary system 714 (16)
3 place	Diseases of the cardiovascular system 140 (4,4)	Diseases of the cardiovascular system 197 (3,5)	Diseases of the cardiovascular system 151 (3,4)

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## TOTAL DYNAMICS OF CHILD MORTALITY RATES IN THE REPUBLIC OF SAKHA (YAKUTIA) FOR THE PERIOD 2006-2015

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### ABSTRACT

The article provides a retrospective analysis of child mortality in the Republic of Sakha (Yakutia) for the period 2006-2015. According to the analysis, there is an evolution of child mortality rates, a steady trend towards a decrease in child mortality rates for many groups of diseases, the presence of gender differences in the structure of child mortality, high child mortality rates in the Arctic regions of the Republic of Sakha (Yakutia).

Insertion of high-tech methods of medical care, input of pediatric and prenatal centers played a huge role for decreasing child mortality rate. Especially it is up-to-date issue in the conditions of the Arctic region, where children's destinies are sometimes resolved by long distance and possibility of ambulance aircraft. Sufficiently huge number of child and adolescent mortality in RS (Y), due to external causes, makes social component of loss. Thus, in the modern stage of development of the Republic of Sakha (Yakutia) the peculiarities of child mortality include, at first, huge demographic significance, at the second-dependence on social life conditions. Because child health is a social category, child mortality rate and structure are integral criterions of population life quality rating and the quality of medical care in the region.

**Keywords:** children, mortality rate, Republic of Sakha (Yakutia), Arctic, injuries and poisoning, external causes.

**Introduction.** Children's and adolescents' health care and its' preservation is one of the main state problems, solving of it provides presence of work force and defensive potential of a country. Convention on the Rights of the Child, which is undertaken almost in all countries of the world, involves realization of wide range of legislative, administrative and other measures for serving of the interests of children, first of all, of their health care. The problems of health preservation, decrease of death rate and children's disability were declared as priority directions by the President of the Russian Federation [2, 3]. The problem of child mortality assumes an up-to-date importance [1].

Nowadays, it is evident, that the fact of medical care is not the only issue in the strategy of national development that is responsible for healthcare, because the main reasons, determining children's ill-being, refer also to social and economic spheres.

The **aim** of the study was to present the evolution of child mortality rates for the period 2006-2015 in the Republic of Sakha (Yakutia).

**Materials and methods.** We analyzed child mortality rate by all disease structure, according to the data of the official statistics of Yakut Republican Medical informative-analytic center for the period 2006-2015.

**Results.** Nowadays the decreasing of child mortality rate is one of the main issues of the demographic development in the Republic of Sakha (Yakutia). For the period 2006-2015 common child mortality rate had decreased. Thus, in 2006 it was 1,5 %, in 2006 and at the beginning of 2015 reached a historic low of 0,7 %.

Mortality rates of male children had increased in dynamics: in 2006 - 61%, in 2015 - 59% (Table 2).

Primary analysis of mortality's age-

**Child mortality in the Republic of Sakha (Yakutia) for the period 2006-2015**

Rate	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total children's death 0-17 years	412	387	361	280	232	206	220	220	217	194
Mid-year child population 0-17 years	261.6	265.2	259.0	251.6	250.6	252.9	253.7	254.9	256.9	259.6
Child mortality rate per 1.000 children	1.5	1.4	1.3	1.1	0.9	0.8	0.8	0.8	0.8	0.7

specific structure within 10 years had found out sustained tendency of child mortality's decrease in all ages group. The Table 3 shows the significant changes in the structure of total child mortality since 2006, thus, the ratio of child mortality of 0-1 ages had decreased, the mortality rates of 15-17 ages' children were stable, and we noted the tendency of increasing child mortality of 1-4, 5-9, 10-14 ages (Table 3).

According to the data, in 2006 we could find in the structure of 412 total child mortalities the following disease classes: perinatal causes are prevailed (154 incidents), then consequences of external causes (137), and on the third place - congenital malformations, deformations and chromosomal abnormalities (56).

In 2015 the structure of 194 total

**Gender differences of child mortality in the Republic of Sakha (Yakutia)**

Years	Boys	Girls
2006	254 (61,65)	158 (38,35)
2007	244 (63,05)	143 (36,95)
2008	209 (57,89)	152 (42,11)
2009	160 (57,14)	120 (42,86)
2010	136 (58,62)	96 (41,38)
2011	132 (64,08)	74 (35,92)
2012	140 (63,64)	80 (36,36)
2013	148 (67,27)	72 (32,73)
2014	133 (61,29)	84 (38,71)
2015	116 (59,79)	78 (40,21)

**Age pattern of child mortality in 2006-2015. %**

Year	0-1 year	1-4 years	5-9 years	10-14 years	15-17 years
2006	53.64	13.83	8.50	9.47	14.56
2007	55.81	14.73	7.75	7.75	13.95
2008	57.89	13.57	5.82	5.82	16.90
2009	38.57	13.93	11.79	12.86	22.86
2010	34.48	15.95	13.79	12.07	23.71
2011	36.89	14.08	8.74	11.17	29.13
2012	38.64	22.27	11.82	12.73	14.55
2013	41.82	15.45	11.82	15.00	15.91
2014	39.17	15.21	9.68	12.44	23.50
2015	39.18	17.53	15.46	13.40	14.43

Table 4

Infant mortality rate dynamics in 2006-2015 per 1000 child population

	Total	Certain infectious and parasitic diseases	Neoplasms	Diseases of the blood and blood-forming organs	Endocrine diseases	Diseases of the nervous system	Diseases of the circulatory system	Diseases of the respiratory system	Diseases of the digestive system	Diseases in the perinatal period	Congenital malformations	Symptoms, signs and abnormal clinical and laboratory findings	Injury and poisoning	Consequences of external causes	Diseases of the genitourinary system	Diseases of the skin and subcutaneous system	Diseases of the musculoskeletal system and connective tissue
2006	1.535	0.030	0.048	...	0.019	0.034	0.019	0.045	0.019	0.574	0.209	0.030	...	0.510	...	...	...
2007	1.472	0.015	0.027	0.004	0.011	0.065	0.030	0.068	0.004	0.487	0.183	0.095	...	0.475	0.008	...	...
2008	1.399	0.015	0.023	...	...	0.054	0.008	0.054	0.004	0.496	0.221	0.043	...	0.473	0.004	0.004	...
2009	1.101	0.024	0.020	0.004	0.008	0.063	0.075	0.055	0.008	0.114	0.083	0.122	0.499	0.016	0.004	...	0.008
2010	0.918	0.028	0.028	0.008	...	0.087	0.055	0.055	0.008	0.047	0.044	0.071	0.479	0.004	...	...	0.004
2011	0.815	0.012	0.032	0.008	0.004	0.063	0.059	0.040	0.012	0.071	0.059	0.055	0.395	0.004	...	...	...
2012	0.867	0.016	0.004	0.008	0.004	0.083	0.059	0.051	0.020	0.067	0.075	0.067	0.406	...	0.008	...	...
2013	0.863	0.016	0.012	0.008	0.004	0.125	0.078	0.039	0.004	0.094	0.024	0.098	0.345	0.012	0.004	...	...
2014	0.844	0.012	0.016	...	0.004	0.078	0.121	0.070	0.008	0.125	0.027	0.047	0.339	...	...	...	...
2015	0.747	0.019	...	...	...	0.108	0.058	0.062	0.023	0.081	0.019	0.039	0.339	...	...	...	...

child mortalities included following disease classes: at first -injury and poisoning (88 incidents), on the second place - diseases of the nervous system (28), then perinatal causes (21).

The total child mortality rate decreased in 2015 from 1,535 to 0,747 per 1000 children (Table 4). In 2006 the most significant increase was found in the following disease classes, such as diseases in the perinatal period, consequences of external causes and congenital malformations. In 2015 we noted the greatest increase for such disease classes, like injury and poisoning, diseases of the nervous system, diseases in the perinatal period. Thus, there is an evolution of child mortality rates, connected with many factors of society development and health-care system.

There is the highest mortality rate in the Arctic region of the Republic of Sakha (Yakutia) (Table 5).

**Conclusion:** According to the analysis of child mortality rates in the RS (Ya) there is an evolution of many groups of diseases. As a whole, child mortality rate has clearly decreased following the common pattern [3- 5]. In fact all differences in the structure of child mortality show real innovations and daily hard work of republican pediatric care.

Insertion of high-tech methods of medical care, input of pediatric and perinatal centers played a huge role for decreasing child mortality rate. Especially it is up-to-date issue in the conditions of the Arctic region, where children's destinies are sometimes resolved by long

Table 5  
Infant mortality rate dynamics in 2006-2015 per 1000 child population according to the regions of RS (Ya)

Region	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Yakutsk	1.320	1.070	1.179	0.797	0.650	0.571	0.567	0.750	0.781	0.734
Arctic	2.486	2.114	2.000	1.588	1.754	2.222	1.647	1.607	1.257	1.024
Industrial	1.356	1.317	1.115	0.854	0.842	0.581	0.796	0.553	0.806	0.698
Agrarian	1.598	1.815	1.639	1.302	1.065	0.943	1.014	1.093	0.742	0.750
Mixed zone	1.657	1.472	1.524	1.494	0.817	0.691	0.900	0.709	1.119	0.714
Total	1.535	1.472	1.399	1.101	0.918	0.815	0.867	0.863	0.844	0.747

distance and possibility of ambulance aircraft. Sufficiently huge number of child and adolescent mortality in RS (Y), due to external causes, makes social component of loss. Thus, in the modern stage of development of the Republic of Sakha (Yakutia) the peculiarities of child mortality include, at first, huge demographic significance, at the second - dependence on social life conditions. Because child health is a social category, child mortality rate and structure are integral criterions of population life quality rating and the quality of medical care in the region.

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## RISK FACTORS FOR THE DEVELOPMENT OF METABOLIC SYNDROME AMONG EMPLOYEES OF RIVER TRANSPORT OF YAKUTIA

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#### ABSTRACT

221 employees of river transport of Yakutia at the age 20-49 years old were examined simultaneously. Metabolic syndrome (MS) was verified in 7.7% of employees of non-indigenous nationality.

One of the most significant risk factor for MS was the age ( $F = 8.24$ ,  $p = 0.005$ ), 58.8% of people with MS belong to the age group from 40 to 49 years old. A sign of disadaptation of an organism - metabolic disorder was observed among people with the experience of 10 and more years. The degree of disorder of metabolic processes is mostly noticed among employees of non-indigenous nationality with an experience of residence in Yakutia of 15-20 years. Revealed age, severe arterial hypertension and the degree of dyslipidemia among river transport employees with MS in comparison with the population with MS indicate the acceleration of mechanisms of metabolic disorder in Yakutia.

**Keywords:** metabolic syndrome, river transport, Yakutia.

**Introduction.** WHO experts described the metabolic syndrome (MS) as a «pandemic of 21st century». Prevalence of MS is 20-40%. It is more common among middle-aged and older people (30-40%). Cardiovascular morbidity and mortality among people with MS are significantly higher than among those without MS. The presence of MS in 3-6 times increases the risk of developing both 2 type of diabetes and hypertension. MS is associated with a subclinical lesion of vital organs. MS is characterized by an increase of visceral fat, a decrease in the sensitivity of peripheral tissues to insulin and hyperinsulinemia, which cause the development of violations of carbohydrate, lipid, purine metabolism and arterial hypertension [8].

As in conditions of the Far North discomfort factors act continuously, depleting the adaptive reserves of the body, the risk of developing metabolic disorder increases, it leads to the formation of pathology [4, 6]. The formation of a specific «polar metabolic type» [5] among northerners are postulated, which is characterized by a complex restructuring of the hormonal-metabolic profile, active use of lipid energy carriers, a decrease of carbohydrates as energy substrates and a change in the need for vitamins. It is shown that there are significant differences in metabolic processes among migrants unadapted to the North and

natives of the North, which can manifest themselves in the specific features of migrants and natives [1].

The specific nature of the operation of the floating structure of river vessels has stringent requirements for the health of workers in the fleet. The shortcomings in the organization of the regimes of labor, life, food, habitation on ships, etc., have a significant effect on the morbidity of crews. The leading factors in this are the impact of occupational hazards - noise, vibration, high humidity, various climatic and geographical and meteorological factors. In addition, the employees of water transport have high psychoemotional load [13]. According to Petrova T.B. and co-authors [2] in addition to climatic and geographic factors, there are specific occupational and socio-environmental factors, which influence on the floating crew of the Northern water basin, which doubles the probability of disturbances in metabolic processes, especially carbohydrate and lipid metabolism, among ship specialists. Due to increasing age and work experience, the activity of cholesterol esterification decreases, imbalance of lipid transport system and carbohydrate metabolism is increased, more noticeable among seamen, river birds and fishermen. According to the comparative analysis of the main causes of mortality in the Republic of Sakha (Yakutia) at the working age of 2005-2011,

it was shown that the former population died more often than indigenous people from diseases of the circulatory system, including acute myocardial infarction and malignant neoplasms. According to the results of studies conducted in the Republic of Sakha (Yakutia), the frequency of metabolic syndrome (MS) is higher in non-indigenous residents than in indigenous ones [9]. The intensification of the lipid metabolism necessary for adaptation to the climatic and geographic conditions of the North with insufficient replenishment of body reserves, can lead to pre-pathological changes in the body. Thus, the study of the characteristics of metabolic processes of the newcomers who are working in the water transport industry of Yakutia is an urgent task for the development of therapeutic and preventive measures for early detection of risk groups. **The aim** of this study was to estimate the features of metabolic syndrome among river transport workers of Yakutia, depending on the medical and social factors, ethnicity and length of stay.

**Material and methods of investigation.** During the planned medical examination, we examined 221 water transport workers of the Republic of Sakha (Yakutia) at the age of 20 to 49 years (mean age  $35.03 \pm 7.95$  years) (men - 184, women - 37). There were 25 people of the indigenous nationality (Yakut people - 21, indigenous people of the North -



4). The non-indigenous population was represented by 196 people (Russians, Ukrainian, Tatar and many others), 85 of them turned out to be born in Yakutia. 111 people arrived from other regions of Russia and the CIS. Depending on the length of stay in Yakutia, they were distributed as follows: up to 1 year - 3 people; up to 5 years - 13; from 5 to 10 years - 15; from 10 to 15 years - 12; from 15 to 20 years - 17; more than 20 years - 51 people.

To identify the features of the metabolic syndrome among river transport workers, a comparative analysis was carried out with selective allocation (Lensky District, Republic of Sakha (Yakutia)), consisting of alien men ( $n = 20$ ).

Blood for biochemical research was taken from the ulnar vein in the morning on an empty stomach. Laboratory research was conducted in conditions of constant internal and external quality control. Activity of aspartate and alanine aminotransferases (asAT, ALAT), alkaline phosphatase, gamma-glutamyltransferase ( $\gamma$ -HT), lactate dehydrogenase (LDH), creatine kinase, glucose levels, total cholesterol (cholesterol), high-density lipoprotein cholesterol (HDL-C), triglycerides were performed by the enzymatic method on the automatic biochemical analyzer CobasMiraPlus by LaRoche (Switzerland) using Biocon reagents (Germany). The levels of low-density lipoprotein cholesterol (LDL-C) and cholesterol of very low density lipoproteins (C-VLDL) were calculated by the formula Friedewald et al. [14]. The coefficient of atherogenicity was calculated by the formula proposed by Klimov A.N. [3]:  $Ka = (C-C-HDL) / HDL-C$ . For hypercholesterolemia, the level of total cholesterol  $\geq 5.0$  mmol / L was taken, elevated LDL cholesterol level  $\geq 3.0$  mmol / L, reduced level of HDL-C  $\leq 1.0$  mmol / L among men and HDL-C  $\leq 1.2$  among women. To hypertriglyceridemia, the level of TG  $\geq 1.7$  mmol / l was referred. The presence of the MS among the examined individuals was verified according to the criteria of the Russian Scientific Society of Cardiology (2010).

The main sign of the diagnosis of metabolic syndrome was abdominal obesity, in which the waist circumference is more than 80 cm among women and more than 94 cm among men. Additional criteria for our study were: arterial hypertension (BP  $\geq 130 / 85$  mmHg) and an increase in the level of TG  $> 1.7$  mmol / l.

The study was approved by the decision of the local ethical committee at the Federal State Budget Scientific Institu-

tion "Yakut Scientific Center of Complex Medical Sciences" and carried out from the consent of the subjects in accordance with the ethical norms of the Helsinki Declaration (2000). In the process of conducting the statistical analysis, test for the distribution of the quantitative indicators was carried out according to the Kolmogorov-Smirnov test. The data are presented in the form of  $M \pm m$ , where  $M$  is the mean value,  $m$  is the standard error of the mean value.

When comparing the quantitative indicators of the groups, the significance of the differences was assessed using the Student's t-test for the normal distribution and the Mann-Whitney test for the abnormal distribution. To compare the frequencies of qualitative characteristics in unrelated groups, the  $\chi^2$  criteria were applied. The results were considered to be statistically significant with the values of the achieved significance level  $p < 0.05$ .

**Results of the study and its discussion.** MS was diagnosed among 17 patients, (16 men and 1 woman), which was 7.69% of the total sample ( $n = 221$ ) of the examined individuals. It should be noted that among the representatives of the indigenous nationality, MS was not identified; all 17 people were representatives of the newcomers. 7 men were born in Yakutia, 8 people had a length of residence in Yakutia for more than 20 years, 1 person was from 15 to 20 years old and 1 person was from 5 to 10 years old. There was only one 48-year-old woman with MS, native of Yakutia, who was of non-indigenous nationality. Analysis of the frequency of MS, depending on the position and the profession, did not reveal any significant differences. This pathology was detected among 4 steering motorists (8.8% of all 49 steering motorists); 3 captains (15% out of 20); 3 mechanics (20% out of 15), 2 administrative and management personnel (10.5% out of 19), 1 gas electric welder (33.3% out of 3), 1 skipper (33.3% out of 3), 1 cooker (5.88% out of 17), 1 coast worker (7.7% out of 28).

Single-factor variance analysis showed significant dependence of MS frequency on age ( $F = 8.24$ ,  $p = 0.005$ ), married life ( $F = 7.98$ ,  $p = 0.005$ ), duration of occupational hazard ( $F = 6.25$ ,  $p = 0.013$ ), as well as on housing conditions, i.e. MS is more common among people living in

comfortable apartments ( $F = 4.65$ ,  $p = 0.032$ ). Comparative analysis found that the mean age ( $40.41 \pm 7.67$  years) of people with MS ( $n = 17$ ) was statistically significantly higher ( $p = 0.005$ ) than of those without MS ( $34.58 \pm 7.82$  years) ( $n = 204$ ). As it can be seen from the presented figure 1, the highest frequency of MS was found in the age group from 40 to 49 years old and constituted 13.5% ( $n = 10$ ) of all people of this age group; in the group of people from 30 to 39 years old - 4.82% ( $n = 4$ ), in the group from 20 to 29 years old - 4.68% ( $n = 3$ ). It should be noted that 58.8% of people with MS (10 people out of 17) were in the age group from 40 to 49 years old.

For further analysis of the features of the formation of MS among river transport workers, we excluded indigenous residents and women from the general sample ( $n = 221$ ), MS was detected in 100% of cases among the newcomers population and in 94% of cases in men.

To study the metabolic characteristics, depending on the length of stay, four comparison groups were formed according to the age: group 1 - 11 men with a residence period from 1 to 5 years old (mean age  $33.63 \pm 1.97$ ); group 2 - 12 men from 5 years to 10 years old ( $31.83 \pm 1.91$ ); group 3 - from 10 to 15 years old ( $32.40 \pm 2.77$ ) and group 4 - from 15 to 20 years ( $33.06 \pm 1.43$ ). In these comparison groups we did not include arrivals from other regions and people who were born in Yakutia ( $n = 67$ ), because adaptation mechanisms to the conditions of the North will to some extent be formed and may have significant differences; people who lived in Yakutia for up to 1 year ( $n = 3$ ) due to the small sample size; people who have lived more than 20 years ( $n = 43$ ) as the mean age ( $40.27 \pm 1.05$  years) was statistically higher than in other comparison groups.

It is known that the main task of the organism in the process of adaptation to the climatic and geographic conditions of high latitudes is the mobilization

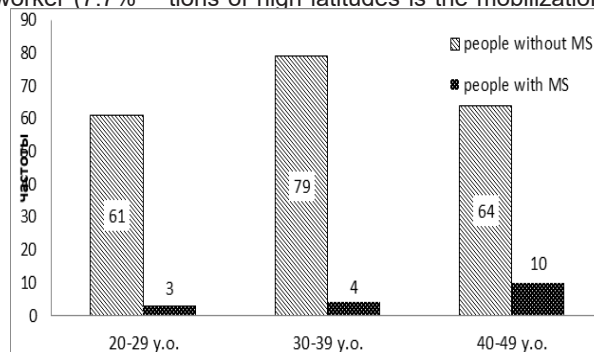


Fig.1. Grouping of people according to their age

Table 1

**Biochemical parameters of blood in non-indigenous men - river transport workers, depending on the length of stay in Yakutia**

Index, reference values	Group				The Importance of Differences
	1 1-5 y.o. n=11	2 5-10 y.o. n=12	3 10-15 y.o. n=10	4 15-20 y.o. n=15	
Age, y.o.	33.63±1.97	31.83±1.91	32.40±2.77	33.06±1.43	
Lactate dehydrogenase, (225-450 U / l)	335.9±15.9	376.5±22.5	366.0±20.7	374.0±11.59	0.006 <sup>##</sup>
Creatine phosphokinase, (< 190 U / l)	110.8±11.1	150.2±13.91	116.8±13.96	117.7±20.0	0.043*
Alkaline phosphatase, (< 258 U / l)	193.2±15.28	205.6 ±12.08	187.8±17.7	194.20± 13.8	
Gamma-glutamyltransferase, (11 to 50 U / l)	23.00±2.42	45.4±8.25	53.6±23.58	45.6±5.23	0.029* 0.002 <sup>##</sup>
ALT, (< 30 U / l)	11.81±1.12	22.2 ± 4.53	20.8±4.43	24.46±5.6	0.05* 0.044 <sup>##</sup>
AsAT, (< 40 U/l)	20.36±1.28	28.20±6.43	34.88±8.9	26.53±5.3	
Coefficient de Ritis, (the norm is 1.3 - 1.5)	1.81±0.13	1.37±0.14	1.87 ± 0.26	1.30±0.14	0.042* 0.048** 0.019 <sup>##</sup>
Glucose, (3.3 to 5.5 mmol / l)	4.95±0.14	4.64±0.12	5.00±0.16	5.18±0.2	0.082 <sup>#</sup>
Triglycerides, (0.5-1.7 mmol / l)	1.26±0.24	1.10±0.15	1.55±0.25	1.27±0.12	
Cholesterol, (3.6-6.5 mmol / l)	4.27±0.26	4.52±0.14	5.05±0.28	5.27±0.28	0.002 <sup>##</sup> 0.028 ° 0.036 <sup>°°</sup>
HDL-C, (0.78-2.2 mmol / l)	1.13±0.14	1.18±0.12	1.18±0.08	1.34±0.09	
LDL-C, (1.68-4.53 mmol / l)	2.79±0.29	2.82±0.15	3.40±0.27	3.49±0.25	0.085 <sup>#</sup> 0.087 <sup>##</sup> 0.04 <sup>°</sup>
HS-VLDL, (0.8-1.5 mmol / l)	0.63±0.11	0.50±0.07	0.65±0.11	0.61±0.10	
The coefficient of atherogenicity, (< 3)	3.47±0.52	3.22±0.27	3.46±0.47	3.60±0.47	

\*-between 1 and 2 group; # - between 2 and 3 group; \*\* - between 3 and 4 group; ## - between 1 and 4 group; ° - between 2 and 4 group; °° - between 1 and 3 group

of resources and the enhancement of energy metabolism in general, and the activity of the organism participating in metabolic reactions can be judged on the functional state of the organism [11]. The comparative analysis of biochemical parameters, depending on the length of stay in Yakutia, showed that the activity of the main enzymes (creatine phosphokinase, lactate dehydrogenase and alkaline phosphatase) is significantly more pronounced among men of the second group than among other groups indicating the intensity of biochemical processes.

Thus, the concentrations of creatine phosphokinase ( $p = 0.043$ ),  $\gamma$ -HT ( $p = 0.029$ ), and ALT ( $p = 0.05$ ) among men of the 2 group were significantly higher than among men of group 1 (Table 1).

There are low values of the enzyme level among men of the 1<sup>st</sup> group in comparison with other groups indicating signs of an emergency phase of adaptation. In this phase, the molecular processes in the cells and membranes of the body do not change; it is required significantly more time for their thorough restructuring. The increased activity of key enzymes among men of the 2<sup>nd</sup> group corresponds to the transition phase of adaptation, for which the intensity of metabolic processes is typical for increasing the energy, plastic and protective maintenance of the organism. Considering the fact that creatine phosphokinase is considered to be an absolutely stress-dependent enzyme and an indicator of the realized energy potential due to the synthesis of a unique endogenous membrane protector of creatine phosphate [11], it can be assumed that non-indigenous men of the 2 group with a residence period of 5-10 years experience a strain of metabolic processes in the greatest degree in comparison with other groups. With different intensity of metabolic processes, one can judge the prevalence of catabolic and anabolic metabolic pathways by the De Ritis coefficient (the ratio of ASAT to ALAT), the adaptation range of which varies from 1.2 to 1.6, its reference value is 1.5. In our study, the de Ritis coefficient was significantly different among compared groups, so in men of the 1<sup>st</sup> group and of the 3<sup>rd</sup> groups its value exceeded 1.8. In the 1<sup>st</sup> group, this indicator was increased due to a low value of ALAT, i.e. decrease in anabolic processes, and in 3 groups - due to increase of ASAT, i.e. catabolic processes. There is an increased content of  $\gamma$ -HT enzymes among non-indigenous men of the 3<sup>rd</sup> group with an experience

of 10-15 years in comparison with other groups, which provides energy-dependent amino acid transport to maintain the level of total protein. It is known that with the enhancement of adaptive mechanisms, glucose appears in the blood due to gluconeogenesis, in its turn, its intensification is possible only with the optimal supply of the necessary substrates for this - amino acids [11].

It should be noted that in the phase of stable adaptation, which is associated with constant voltage of the control mechanisms, the restructuring of the nerve humoral ratios, the formation of new functional systems, adaptive processes can be depleted. Depletion of control mechanisms, on the one hand, as well as cellular mechanisms associated with increased energy costs, leads to disadaptation [7]. With chronic effects on the body of sub-extreme and extreme factors, the role of lipids in energy supply of adaptation reactions increases. The fat-mobilizing effect and the formation of

transport forms of fat-lipoproteins of all classes are intensified [12]. Taking into account the fact that it was revealed content of enzymes  $\gamma$ -HT, AST, glucose, total cholesterol, atherogenic fraction of LDL-C and atherogenicity coefficient among non-indigenous men of the 3<sup>rd</sup> group with the experience of 10-15 years it can be stated about the depletion of adaptive reserves and the development of disadaptation. Violations of carbohydrate and lipid metabolism are most pronounced among people the 4<sup>th</sup> group with a residence time of 15-20 years (Table 1).

Thus, the data obtained by us show that the length of stay in the North is one of the main risk factors for metabolic disorders, i.e. the higher the length of service, the greater the degree of violations.

To assess the characteristics of the metabolic syndrome among river transport workers, a comparative analysis was made between the data of non-indigenous men: river transport workers ( $n = 16$ ) and population sampling ( $n = 20$ ) with

MS. The population sample was chosen during a comprehensive medical survey in the expeditionary conditions of residents of the village of Vitim in the Lensk District, the Republic of Sakha (Yakutia).

The results of the comparative analysis indicate that the mean age ( $38.44 \pm 2.12$  years) among river transport workers is significantly ( $p = 0.001$ ) lower than among population sample ( $53.40 \pm 1.32$  years), which may indicate the earliest formation of the metabolic syndrome among non-indigenous men working in the water transport industry. In terms of anthropometric parameters (height, weight, BMI, waist circumference, hips), a significant difference was revealed only by height ( $p = 0.026$ ). The value of height among river transport workers ( $176.68 \pm 1.26$  cm) was higher than among population group ( $170.35 \pm 2.21$  cm).

The indices of arterial pressure among river transport workers were higher than among population group. Thus, the mean diastolic pressure among river transport workers was significantly ( $p = 0.001$ ) higher ( $94.62 \pm 2.09$  mm Hg), and systolic blood pressure ( $142.00 \pm 2.62$  mm Hg) tended to an increase ( $p = 0.085$ ) in comparison to the population sampling ( $82.00 \pm 0.92$  and  $135.00 \pm 2.94$  mmHg, respectively) (Fig. 2).

There is a significant increase of triglyceride content ( $p = 0.001$ ), total cholesterol ( $p = 0.023$ ), and uric acid ( $p = 0.001$ ) in the serum of river transport workers in comparison with the population sample. They also showed a significant reduction in the content of the antiatherogenic fraction - high-density lipoprotein (HDL-C) ( $p = 0.006$ ) and the associated significant increase in the atherogenic index ( $p = 0.003$ ). The average values of LDL-C and C-VLDL among river transport workers exceed those of the population sample although they do not have significant statistical differences. Thus, the obtained results of a comparative analysis of biochemical parameters indicate an unfavorable atherogenic background among river transport workers in comparison to the population sample (Table 2).

The obtained data to some extent confirm the data of Khasnulin V.I. and co-authors (2011) [12] indicating that lipid metabolism disorders among alien residents of the North, with the impossibility of switching to the northern type of metabolism, become one of the important links in the progression of arterial hypertension in high latitudes.

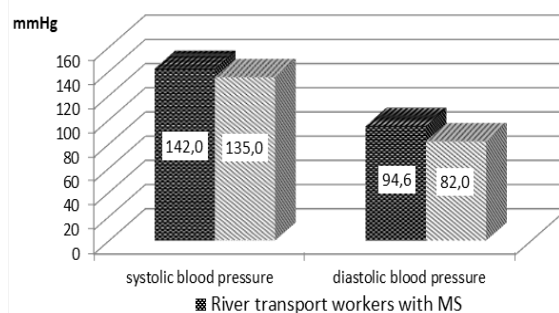
Dyslipidemia is one of the main and most frequently encountered diagnostic

criteria for MS. With respect to MS and coronary atherosclerosis, the high levels of LDL-C and, especially TG, reduced levels of HDL-C are the dominant disturbances in the lipid transport system [9]. Hyperuricemia is one of the most important components of MS and is involved in the pathogenetic mechanisms of atherogenesis, activating the processes of lipoperoxidation with the formation of peroxide-modified LDL-C [9]. Oxidative stress and an increase in the oxidative modification of lipids in the wall of the arteries can play a significant role in the progression of atherosclerosis. It was also found that uric acid is capable to activate the adhesion and aggregation of platelets. These mechanisms demonstrate the active participation of uric acid in the processes of atherogenesis and confirm the significant role of hyperuricemia in the formation of a high risk of cardiovascular pathology in patients with MS.

Undoubtedly, the length of stay of an alien population in the North is one of the main risk factors for the formation of metabolic disorders and leading to pre-pathological conditions.

**Conclusion.** MS was verified in 7.7% of river transport workers, indicated data refer to non-indigenous residents of Yakutia. One of the significant risk factors for MS was the age ( $F = 8.24$ ,  $p = 0.005$ ) of the examined individuals. 58.8% of people with metabolic syndrome were in the age group from 40 to 49 years old.

Among non-indigenous people working in the river transport of Yakutia, the signs of disadaptation of metabolic processes (dyslipidemia, increase in blood glucose) begin to be observed among people with experience of residents of 10 years or more. The degree of disturbance of metabolic processes is most pronounced in newcomers with an expe-



**Fig.2.** Indices of blood pressure among river transport workers and population sampling with metabolic syndrome experience of 15-20 years.

The average age of the river transport workers with MS ( $38.44 \pm 2.12$  years) was significantly lower ( $p = 0.001$ ) than among the population sample with MS ( $53.40 \pm 1.32$  years), which probably indicates early formation of MS among the newcomers working in the branch of the river transport of Yakutia.

Comparative analysis of people with MS indicates that arterial hypertension and degree of dyslipidemia are more pronounced among river transport workers than among population sample, which may indicate a negative impact of working conditions of river transport workers, which provokes acceleration of metabolic disturbances in Yakutia.

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**Table 2**  
**Biochemical parameters of blood in people with metabolic syndrome**

Biochemical parameters	River workers with MS (n=16)	Population sample with MS (n=20)	p= ...
Uric acid. mmol / l	$443.92 \pm 17.14$	$261.58 \pm 21.2$	0.001
Triglycerides. mmol / l	$2.67 \pm 0.32$	$1.24 \pm 0.18$	0.001
Cholesterol. mmol / l	$6.03 \pm 0.29$	$5.24 \pm 0.13$	0.023
HDL-C. mmol / L	$0.99 \pm 0.03$	$1.24 \pm 0.07$	0.006
LDL-C. mmol / L	$3.69 \pm 0.29$	$3.44 \pm 0.23$	
C-VLDL. mmol / l	$1.26 \pm 0.15$	$1.24 \pm 0.18$	
Atherogenicity index	$5.01 \pm 0.42$	$3.44 \pm 0.23$	0.003



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## SPACE WEATHER EFFECTS ON THE FEATURES OF PERSONAL RESPONSE OF VOLUNTEERS IN A MULTIPLE-LATITUDE MONITORING

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### ABSTRACT

The article presents a comparative analysis of psycho-emotional peculiarities of persons from polar, sub-polar and middle latitudes, taking part in multiple-latitude monitoring, in relation to a psychological sensitivity to heliogeomagnetic factors.

64 relatively healthy persons, males and females, have been examined using the following tests: State-Trait Anxiety Inventory (STAI) (Ch. Spielberg, U. Khanin), E. Heim Test, Psycho-Geometric Test. Reactive anxiety and integral index of heliogeomagnetic activity (Kp-index) have been determined by a two-month phase of monitoring, other tests have been checked once in the beginning of a phase. Group I consisted of persons with maximum coincidences in Kp-index peaks and in reactive anxiety. Group II consisted of persons with no coincidences. It is found that the volunteers from the group I and II, as in northern (polar and sub-polar) as in middle latitudes, had a number of similarities depending on a psychological sensitivity to heliogeophysical factors (tending to analyze problems, emotional suppression, agreeableness, purpose). The findings of the study allow organizing patient-specific preventive methods for psycho-somatic diseases and neuroticisms in relatively healthy persons taking into consideration their psychological sensitivity to changes in heliogeomagnetic activity, and the latitude of their place of living.

**Keywords:** heliogeomagnetic activity, anxiety, polar, sub-polar and middle latitudes, stress-overcoming behavior.

**Introduction.** The given research was controlled by a multiple-latitude monitoring of the study of heliogeophysical factors effects on psycho-emotional and somatic (cardiovascular system, primarily) state of inhabitants of auroral (Tiksi), sub-auroral (Yakutsk) and middle latitudes (Saratov). The monitoring is being held simultaneously during two months in fall and/or spring periods (October-November, March-April) – the periods of a maximal activity of heliogeomagnetic factors [5], in groups of volunteers from the given latitudes, with a daily recording for a uniform protocol.

The monitoring started in 2014 and it is a follow-up to the previous unique international project “Heliomed”, which was organized by an interdisciplinary project-team of physics, biologists, informational technologies specialists, psychologists and physicians [1].

A combined research of a psycho-emotional status and of a cardiovascular system condition of volunteers in space weather changes [5].

“Space weather” or “cosmic weather” is a phenomena in an upper atmosphere, in an ionosphere and in the near-Earth environment. Space weather, as well as the weather as a common notion of this word, is characterized by a cycle of calm periods (the minimum of a solar activity cycle) which can be comparable to a stable summer weather, and a cycle of abrupt changes (in high solar activity) which may be analogical to an changeable fall weather. A changeable weather in the near-Earth environment links with

the Earth environment – there are no two days of a kind. So, as a grey rainy day in November differs from a sunny May day, as two days may not be the same from the space weather and its factors point of view [12].

The main targets for heliogeophysical factors are human nervous and cardiovascular systems. During the geomagnetic activity there are: arrhythmia, heart rate changes, BP peaks, blood viscosity and erythrocytes aggregation increases, capillary slow flow, and a number of other pathological changes happen [3, 9].

Alongside with traditional risk factors of cardiovascular pathology developing (smoking, adiposity, hypodynamia, etc.), today there are data about psycho-social risk factors accumulated (anxiety, depression, alexithymia) [4, 6, 8], and data about increased indices of a solar and geomagnetic activity on blood circulation organs diseases [3, 5, 9]. At the same time, complex influence of these factors on physiological and psychological characteristics of healthy people are not enough studied.

Over the last years, there are innovative abilities of registering and analyzing space weather parameters by artificial satellites of the Earth. These data analyze, further studying the effect of the solar and geomagnetic activity parameters on a cardiovascular system and personal psychological features may allow to optimize measures of a primary prevention of cardiovascular diseases leading to a high mortality percent of an adult population on Earth. All these make studying the

effect of heliogeomagnetic factors on a psycho-emotional condition of a healthy person actual.

A detailed studying of personal psychological features of people from polar and middle latitudes from the point of their stress-overcoming behavior differentiated according their spheres and types of personality, with the space weather effect on them, had not been held earlier.

**Aim:** make a comparative analyze of psycho-emotional features and to determine them in persons living in polar, sub-polar and middle latitudes, and taking part in a multiple-latitude monitoring in 2015, in dependence of a presence of a psychological sensitivity to a changeable geomagnetic state.

**Methods of research and objects.** Relatively healthy persons took part in the research – males and females (n=64), age - 44, 8 (40,7; 45,2) years. The observation of the volunteers was organized in a spring monitoring phase in 2015, in March and April, in Saratov (middle latitude), Yakutsk (sub-polar latitude), Tiksi (polar latitude).

To achieve the goal the following tests were used:

- State-Trait Anxiety Inventory (STAI) (Ch. Spielberg, U. Khanin) [2, 7];
- E. Heim Test, building a stress-overcoming behavior [11];
- Psycho-Geometric Test [10].

Reactive anxiety of the volunteers according to Spielberg-Khanin had been determined every day during a two-months observation (March-April), the other tests had been given once at the

beginning of the monitoring phase. An integral parameter of geomagnetic activity had been used daily - Kp-index.

Statistical processing of the findings was done by an application program package Statistica 6.0, Microsoft Excel 7.0. for Windows, checking zero hypothesis of conformity with a normal distribution law based on a Shapiro-Wilk criterion, and following use of nonparametric mathematical methods (as the distribution of variables was non-normal). The data are presented as a median (Me) with values of quartile range (25%, 75%) for samples. Reliability of the used statistical estimating was no less than 95%.

**Results and discussion.** We divided all of the observing persons into two groups depending on coincidence (no less than 60%) in absolute and pinnacled increase of the values of reactive anxiety by Spielberg-Khanin, and Kp-index values. In the group I there were people who had such coincidences – volunteers with a psychological sensitivity to heliogeomagnetic factors changes. In the group II there were volunteers with no coincidences mentioned above – without psychological sensitivity to geomagnetic factors changes.

During the examination of the volunteers living in polar and sub-polar latitudes we established the followings: group I with persons having a psychological sensitivity to changeable heliogeophysical factors consisted of 42,9% (39,2; 43,7) people. In the group II there were 57,1% (52,7; 58,6) persons with no psychological sensitivity.

The results of examination of auroral and sub-auroral inhabitants by the use of E. Heim test are presented below on Pictures 1-3.

From the data on Pic. 1 we can see that in the group II as in the group I adaptive coping-cognitions predominate, which is keeping self-control ( $p \leq 0,05$ ).

As it follows from the data on Pic. 2, the volunteers with a psychological sensitivity to heliogeomagnetic factors changes had chosen adaptive coping-forms more seldom than those one with no sensitivity (in both groups this was optimism), and it's interesting that persons from the group I had chosen mostly non-adaptive coping-behavior – emotion suppression ( $p = 0,04$ ).

As for the choice of behavior coping-responds (Pic. 3), there should be noticed a number of prevailing choice of non-adaptive coping-behavior (retreat) in the group I, and the choice on a par with adaptive (asking for help) and non-adaptive (active escape) coping-behavior in persons from the group II ( $p \leq 0,05$ ).

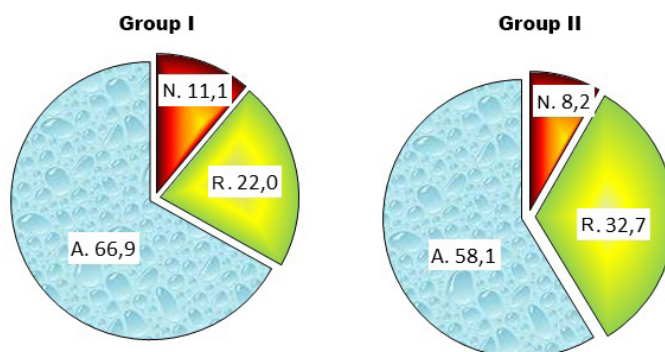
The results of the research with stimu-

lus material of a Psycho-Geometric Test in the observing persons living in northern latitudes are presented on Pic. 4-5.

As we can see from the Pic. 4-5, the volunteers from the both groups living in northern latitudes preferred triangle and refused zigzag ( $p \leq 0,05$ ). Among the inhabitants of middle latitudes taking part in the monitoring, 46,7% (40,6; 47,2) of persons were in the group I, 53,3% (49,3; 54,1) – in the group II.

The peculiarities of building stress-overcoming behavior by E. Heim in the volunteers from Saratov are presented on Pic. 6-8.

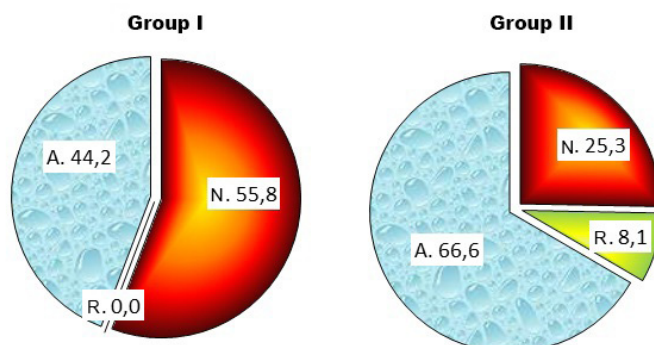
As we can see from the data on Pic. 6, the persons with psychological sensitivity to heliogeomagnetic factors changes, living in middle latitudes, preferred choosing non-adaptive cognitive coping-behavior (dissimulation and submission), the volunteer without sensitivity – adap-



**Pic. 1. Distribution of cognitive coping-strategies in inhabitants of northern (polar and sub-polar) latitudes in groups (%).**

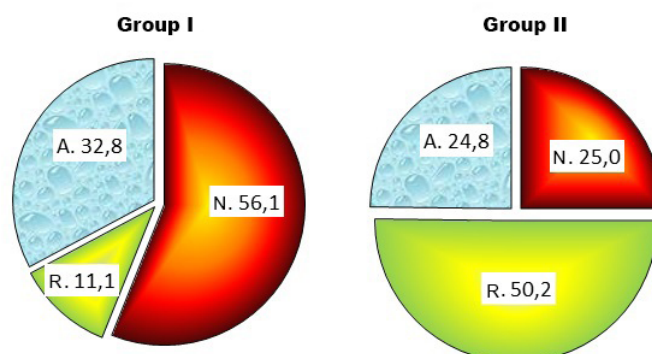
*Note. Notions of coping-strategies kinds: A — adaptation, R — relatively adaptation,*

*N — non-adaptation*



**Pic. 2. Distribution of emotional coping-strategies in inhabitants of northern (polar and sub-polar) latitudes in groups (%).**

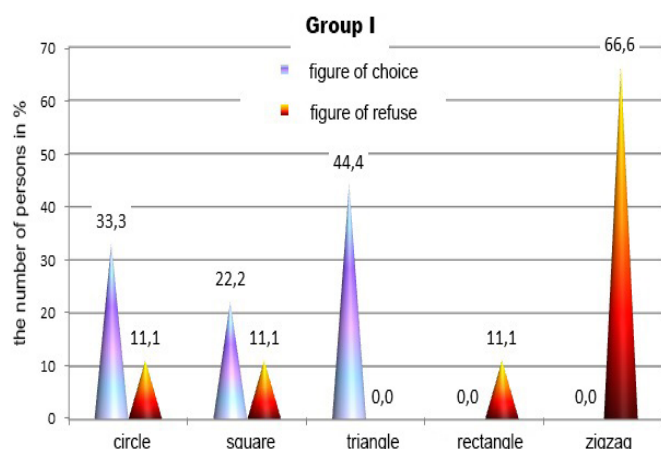
*Note. Values of respond types are the same as for the Pic. 1.*



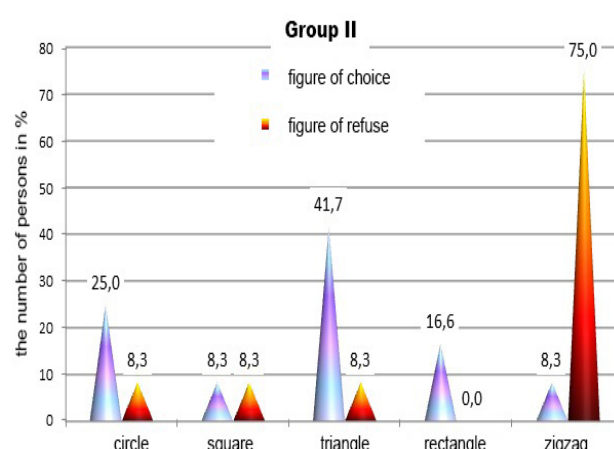
**Pic. 3. Distribution of behavior coping-strategies in inhabitants of northern (polar and sub-polar) latitudes in groups (%).**

*Note. Values of respond types are the same as for the Pic. 1.*





Pic. 4. Results of psycho-geometric tests in inhabitants of northern latitudes in the group I (%).



Pic. 5. Results of psycho-geometric tests in inhabitants of northern latitudes in the group II (%).

tive (problem analyzing and establishing own value) ( $p \leq 0,05$ ).

The volunteers from the group I chose adaptive emotional coping-strategies (optimism, protest) of nearly the same frequency as the persons from the group II (latter ones – only optimism). Among non-adaptive coping-strategies the representatives from both groups, living in middle latitudes, preferred emotional suppression and blamed themselves in any troubles, and what's interesting, persons with no psychological sensitivity to heliogeomagnetic factors did that more often ( $p < 0,05$ ).

As we can see from the Pic. 8, in persons with psychological sensitivity to changeable heliogeomagnetic factors, in building their own coping-behavior, adaptation coping-strategies predominated (asking authority figure for help), and the volunteers without sensitivity chose adaptive (ask for help) and non-adaptive (retreat) coping-behavior in the same frequency.

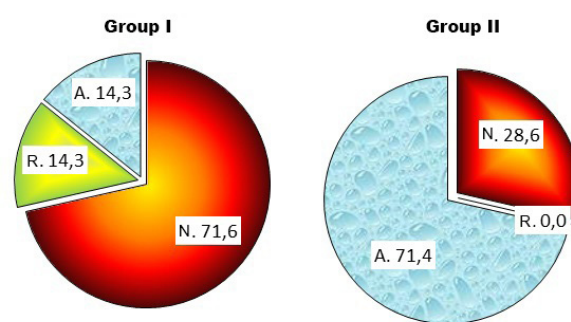
That is interesting to notice that the findings from the volunteers of the group I, living in middle latitude, in work with the stimulus material of the psycho-geometric test, are analogical to the same results from the persons of northern latitudes (group I): they chose triangle and refused zigzag. The representatives of the group

II chose circle and triangle with the same frequency, and refused zigzag and circle ( $p \leq 0,05$ ).

It stands out that on the given stage of the monitoring we established practically the same frequency of episodes of a psychological sensitivity to heliogeophysical activity in persons as from middle as from northern latitudes.

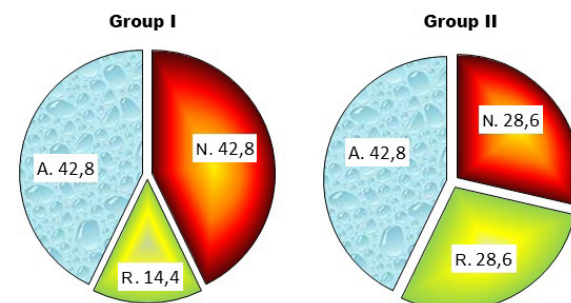
On the base of the findings of a psychological examination, it seems as if inhabitants of polar and sub-polar latitudes, regardless of the presence or absence of a psychological sensitivity to heliogeophysical activity changes, are representatives of a composed manner of behavior, they are serious, organized, highly responsible, tend to analyze problems, they don't get rattled in any situations. At the same time they are optimists, and they are sure as in positive results as in their own possibilities. It stands out that the persons with a psychological sensitivity to heliogeomagnetic factors, comparing to those ones who do not have sensitivity, are more patient and self restrained, have a strong will power, self-esteem, they never ever show off their emotions even if they are ill, and cover all symptoms.

Compared to persons from polar and sub-polar latitudes, between the representatives of the group I



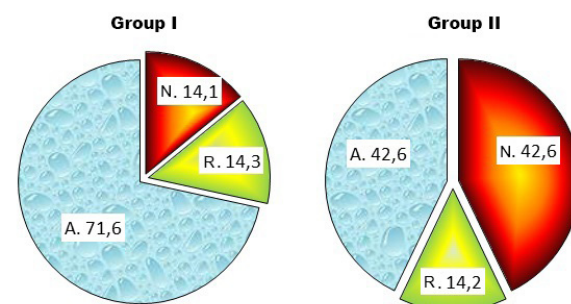
Pic. 6. Distribution of cognitive coping-strategies in inhabitants of middle (Saratov) latitudes in groups (%).

Note. Values of respond types are the same as for the Pic. 1.



Pic. 7. Distribution of emotional coping-strategies in inhabitants of middle (Saratov) latitudes in groups (%).

Note. Values of respond types are the same as for the Pic. 1.



Pic. 8. Distribution of behavior coping-strategies in inhabitants of middle (Saratov) latitudes in groups (%).

Note. Values of respond types are the same as for the Pic. 1.

and II from middle latitudes there is no as much common which is limited by optimism, emotion suppression, submission and asking for help in difficult situation. As for the difference in the groups, we should notice high behavior adaptation in persons with psychological sensitivity to heliogeomagnetic factors, and their less cognitive adaptation, comparing to those who has no such sensitivity. The representatives from the group I more often then those ones from the group II, tended to analyze problems, suppressed emotions, though, protested sometimes, and could dissimulate when they were ill.

Regardless of the latitude, the volunteers with a psychological sensitivity to changeable heliogeomagnetic factors, were kind and purposeful, preferred analyzing cause-and effect relationship of problems, tended to dissimulation and emotion suppression. Those who had no sensitivity were, as a rule, contradictory and tended to ignore problems.

**Conclusion.** From there, in 2015 during monitoring there had been revealed a coincidence of frequency of presence of psychological sensitivity and non-sensitivity in volunteers among inhabitants of northern and middle latitudes, to changes in geomagnetic activity.

On the base of this research there had been established that among the volunteers who took part in multiple-latitude monitoring had as similarities as differences, taking to account the latitude, psychological sensitivity to heliogeophysical factors. Many similar features are subjected, first of all, by the latitude of living, though, there are some close features in volunteers with psychological sensitivity to heliogeomagnetic activity (tendency to analyze problems, suppress emotions, kindness, focus).

*Conflict of interests in the study was not stated.*

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## INDICATORS OF THE CARDIOVASCULAR SYSTEM IN THE CAUCASIAN RESIDENTS OF MAGADAN REGION DEPENDING ON THE TERM OF RESIDING UNDER CONDITIONS OF RUSSIA' NORTHEAST

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### ABSTRACT

The climatic conditions of the North have been forcing the human body to use additional social and biological means of protection against the adverse effects of environmental factors. It should be noted that, first of all, the cardiorespiratory system undergoes the influence of these abiotic factors. In this regard, the purpose of the research was to study and identify the characteristics of the cardiovascular system in young male residents of Magadan Region who differ in terms of residence in the northeast of Russia. 1632 young male subjects aged 17 to 21 and permanently residing in the city of Magadan, were examined in 2005–2017 using standard methods for determining cardiovascular parameters. Depending on the length of residing in the region all the subjects were divided into 4 groups. They represented three generations as well as migrant Caucasians who were not born in Magadan Region but came there from the central regions of the country. Residents of the northeast of Russia with short periods of residence in the North demonstrated a state of stress in the cardiovascular system manifested by an increase in systolic pressure, total peripheral vascular resistance, heart rate, and a decrease in the blood stroke volume. At the same time, the representatives of the 3rd generation had better functioning of the system. They were significantly lower in blood pressure (both systolic and diastolic) and the heart rate. In addition, the subjects of this group had minimal cardiac output, which indicated a more economical functioning of the cardiovascular system in the conditions of the northeast of Russia.

**Keywords:** cardiovascular system, generations of residence in the North, adaptive changes

The territory of Magadan Region that is located in the northeast of Russia (59.33 northern latitude) belongs to the subarctic region (55-66.5 north latitude) according to modern concepts of circumpolar regions [20]. Circumpolar regions create a unique set of negative environmental factors affecting humans, including prolonged and severe cold stress with negative monthly temperatures, which in some regions may drop to  $-40^{\circ}\text{C}$  [20]. Living in the conditions of the northeast of Russia can be considered as life with additional functional tension. So the climatic characteristics of the North are defined by researchers as uncomfortable, severe [1], and even extreme [12] as they make significant demands to the human body, forcing it to use additional social and biological means of protection against unfavorable environmental factors [18].

The physiological mechanisms of adaptation changes in the cardiovascular system under northern conditions have been studied fairly well and are presented in numerous works [3, 4, 7, 19]. The results of such studies are aimed at creating the conditions for maintaining health and increasing the life expectancy of people living and working in the arctic and subarctic climatic zones under

unfavorable natural conditions [4]. At the same time, much less attention is paid to the study of adaptive rearrangements in the activity of the cardiovascular system in different periods of residence under the northern conditions.

The circulatory system serves as a marker of the nature of the adaptation processes in the body and is one of the first to reflect a state of stress, exhaustion, and pathology [10]. Acute exposure to cold is associated with a decrease in peripheral blood flow and an increase in metabolic heat production to maintain body temperature. The vasomotor response of the cardiovascular system is mediated by sympathetic activation directed toward peripheral vasoconstriction which results in the body heat loss decrease at the expense of a decrease in peripheral blood flow [16]. This is a necessary term for the functioning of the cardiovascular system since peripheral cold stress due to sympathetically controlled vasoconstriction increases arterial pressure by increasing the peripheral resistance [17]. Of note that chronic vasoconstriction leads to the development of hypertension [15]. At the end of the 20th and beginning of the 21st centuries, the identification and study of the mecha-

nisms of the development of early stages of hypertension, called "near-disease" or "prehypertension" became of special relevance. This condition is more often demonstrated by young men [14; 22]. According to the authors, one of the pre-nosological conditions is the so-called "high normal pressure" of 130-139 / 85-89 mm Hg [23].

Based on the above, the **purpose** of this work was to study the cardiovascular system in young residents of Magadan region differing in terms of residence in Russia' northeast.

**Materials and methods.** By random sampling, 1,632 young men aged 17 to 21, permanent residents of the Magadan Region, were examined. Depending on the term of residence in the territory of Magadan Region all the examinees were divided into 4 groups. The I group ( $n = 62$ ) included migrant-Caucasians moved here from the central regions of the country and characterized by a short period of residence in the North (average  $7.1 \pm 1.3$  years). We designated this group as the "zero generation". The II group included those born in Magadan Region in the 1st generation from among Caucasians but whose parents were migrants ( $n = 924$ ). The III group included young people born



in the region in the second generation ( $n = 580$ ) whose parents were born in the territory of Magadan region in the 1st generation. And the IV group are the subjects with the longest term of residence in Magadan region, which are representatives of the population that is just starting to form (due to the "relative youth" of our region). They are young males of the third generation ( $n = 66$ ) whose parents belong to the representatives of the 2nd generation. All studies were conducted between 2005 and 2017.

Characteristics of the cardiovascular system were determined using an automatic blood pressure tester Nessei DS-1862 (Japan). The systolic ( $BP_s$ , mmHg) and diastolic ( $BP_d$ , mmHg) values of arterial pressure were measured at rest as well as the heart rate (HR, bpm). In addition, the Starr stroke volume (SV, mL), cardiac output (CO, L/min) and the total peripheral vascular resistance (TPVR,  $\text{dyn}^2 \text{ s cm}^{-5}$ ) were calculated [11].

**Results and discussion.** The parameters of the cardiovascular system in young men with different degrees of adaptation to the conditions of Russia's northeast are presented in the table. Our study has found the young male subjects of the 0th generation to be very close to the upper limit of the normal systolic blood pressure. These values reflected high normal blood pressure [21] and significantly exceeded the indices typical for residents of the central part of the country and the European North [2, 9, 13]. We have concluded before that, modern young male Caucasians of Magadan region are oriented towards hypertensive values in their blood pressure [6]. The reaction of the cardiovascular system in individuals with the shortest period of adaptation to the conditions of the northeast of Russia was due to the increased systolic blood pressure. We assumed the latter to be a compensatory mechanism under the action of low ambient temperatures. It should be noted that the young male residents among the representatives of the third generation characterized by the longest period of residence in the Northern conditions demonstrated

the lowest indices of the arterial pressure against the backdrop of the lowest values of the total peripheral resistance of the vessels.

Statistically higher heart rate indices were observed in groups of young men of the 0th, 1st, and 2nd generation, relative to their age mates from among the representatives of the 3rd generation. It is known that a faster heart rate is potentially unfavorable for the optimal circulatory state, in particular, due to the shortening of the period of the diastolic phase and the increased tension with respect to the cardiac output (CO) which is metabolically much more expensive for the body, requires a significant increase in oxygen intake [5], and indirectly may indicate a reduced effectiveness in the work of the cardiovascular system. Cardiac output is an extremely important variable in the cardiovascular system which is constantly regulated so that the this system can satisfy the gas transporting needs of the organism at particular time, and the higher the potential energy expenditure of the organism, the more pronounced the proportional increase in CO. From this position, the lower values of this indicator in the group of young men, the representatives of the third generation who are most adapted to the abiotic factors of the North, have become clear, which is consistent with the principle of economizing the energy functions of the organism in conditions of extreme climatic characteristics. In the series from the 0th generation to the 3rd generation, a significant dynamics of the increase in the blood stroke volume was noted, which reflects the effective provision of the blood cardiac output circulation due to the high value of the stroke volume against the significantly lower values of heart rate in the young male subjects of the 3rd generation.

**Conclusion.** The analysis has shown, that Russia's northeast subjects with short periods of residence in the North have been experiencing the state of stress in the cardiovascular system manifested by an increase in systolic pressure, total peripheral vascular resistance, heart

rate, and a decrease in the blood stroke volume. At the same time, the representatives of the 3rd generation have demonstrated more optimal parameters in the work of the system, which is seen in significantly lower values of the arterial pressure (both systolic and diastolic), and the heart rate. In addition, the subjects of this group have had minimal blood cardiac output, which indicates a more economical functioning of the cardiovascular system under Russia's northeast conditions and characterizes the strategic orientation of adaptive rearrangements associated with the body functional systems' energy minimization under the cold factor, which is well shown in animal studies [8]. In this regard, the direction of changes in the circulatory system has become reasonable. The tension of the system functioning in migrants proved to be significantly higher than that of representatives of the 1st and the subsequent generations. At the same time, the vector of functional physiological rearrangements among migrants and different generations of the north born Caucasians allows us to state that in the current conditions, a new population is forming in the northeast of Russia which we have designated as rooted individuals.

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**Cardiovascular system indices in subjects with different rates of adaptation to the conditions of the northeast of Russia ( $M \pm m$ )**

Parameter	Examined subjects				Significance of differences among examined groups					
	0th generation (1). $n = 56$	1st generation (2). $n = 924$	2nd generation (3). $n = 580$	3rd generation $n = 66$	I-II	II-III	III-IV	I-III	I-IV	II-IV
BPS. mmHg	129.7±0.6	128.0±0.4	128.0±0.4	127.8± 0.8	$p=0.18$	$p=1.00$	$p=0.94$	$p=0.18$	$p<0.05$	$p=0.86$
BPD. mmHg	77.1±1.0	76.0±0.3	75.0±0.3	71.8 1.2	$p=0.29$	$p<0.05$	$p<0.001$	$p<0.05$	$p<0.001$	$p<0.001$
HR. bpm	78.2±1.1	79.6±0.4	79.0±0.5	71.8 1.6	$p=0.61$	$p=0.34$	$p<0.001$	$p=0.32$	$p<0.001$	$p<0.001$
SV. mL	69.8±1.3	70.4±0.3	71.1±0.3	75.1 1.0	$p=0.48$	$p=0.09$	$p<0.001$	$p=0.19$	$p<0.001$	$p<0.001$
CO. L/min	5594.5±92.5	5575.2±34.3	5510.6±43.8	5362.3±96.6	$p=0.82$	$p=0.24$	$p=0.26$	$p=0.39$	$p<0.05$	$p<0.05$
TPVR. $\text{dyn}^2 \text{ s cm}^{-5}$	1579.6±46.1	1532.9±12.5	1467.4±14.8	1434.1±31.1	$p=0.32$	$p<0.05$	$p=0.33$	$p<0.05$	$p<0.05$	$p<0.05$

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## USAGE OF THE FIXED-DOSES COMBINATIONS FOR DRUG THERAPY OF ARTERIAL HYPERTENSION IN NORTHERN REGIONS OF THE FAR EASTERN FEDERAL DISTRICT

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### ABSTRACT

**Aim.** To analyze the usage of the fixed-doses combinations for treatment of arterial hypertension in three northern regions of the Far Eastern Federal District.

**Material and methods.** The pharmacoepidemiological study of realization of antihypertensive drugs in the pharmaceutical organizations of the Magadan region, Kamchatka Krai, the Sakha Republic (Yakutia). The studied period was 2013-2017. Total sales were calculated based on the amount of drugs and defined daily doses, acquired by patients. The range of international nonproprietary names has been divided into therapeutic classes. Further calculation of indicators in group for each combination was carried out. The analysis was performed with usage of Microsoft Office of Excel 2015.

**Results.** In a therapeutic class of combinations  $\beta$ -blockers with diuretics or calcium channel blockers the combination atenolol+chlortalidone remained the leader in three regions. Shares of sales of other international nonproprietary names were insignificant, and did not exceed totally 10%. Valsartan+amlodipin had the greatest indicators of realization in the therapeutic class of angiotensin II antagonists with calcium channel blockers. Among combinations of angiotensin II antagonists and diuretics, the combination of losartan+hydrochlorothiazide had more than a half of the acquired defined daily doses. Since 2017 in the Sakha Republic (Yakutia) were more actively used valsartan+hydrochlorothiazide, azilsartan medoxomil+chlortalidone. In a therapeutic class of angiotensin-converting-enzyme inhibitors with calcium channel blockers in the Magadan region and in the Sakha Republic (Yakutia) the leader of the market was the combination of lisinopril+amlodipine, in Kamchatka Krai - perindopril+amlodipine. Acquisition of the drugs containing ramipril and amlodipine has increased in all three regions. In a therapeutic class of combinations of angiotensin-converting-enzyme inhibitor with diuretics, the redistribution of preferences from drugs containing enalapril+hydrochlorothiazide in favor of perindopril+indapamid was observed. The combinations lisinopril+hydrochlorothiazide had the considerable share of sales in the Sakha Republic (Yakutia). Usage of a combination of hydrochlorothiazide+triamterene and drugs of a reserpine is characteristic of the Magadan region and Kamchatka Krai. In the Sakha Republic (Yakutia), in comparison with other explored regions, triple-component drugs are more actively applied.

**Conclusions.** The greatest part of realization of the defined daily doses of the modern antihypertensive fixed-doses combinations was the share of only seven international nonproprietary names, on condition of presence in the pharmaceutical market of 43 variants. Current situation proves expediency of prescription of the applied schemes of drugs therapy, taking into account the available range of drugs in the pharmaceutical organizations of regions.

**Keywords:** arterial hypertension, fixed-doses combinations, pharmaceutical market, Far Eastern Federal District, defined daily dose, epidemiology.

#### List of reductions:

$\beta$  – AB –  $\beta$ -blockers

AH – arterial hypertension

BP – arterial blood pressure

AC – calcium channel blockers

ARA – angiotensin II antagonists

D – diuretic

FEFD – the Far Eastern Federal District

ACE inhibitor – angiotensin-converting-enzyme inhibitor

INN – international nonproprietary name

FDC – the fixed-dose combination

**Introduction.** The high morbidity of cardiovascular system, risk of development of fatal complications, results of modern randomized studies, data of meta-analyses, registration in the pharmaceutical market of new drugs and improvement of their forms of usage, cause need of systematic revision of the existing recommendations, standards, other regulations regulating approaches of experts to drugs therapy [1]. The Far Eastern Federal District (FEFD) is also characterized by high rates of presence of cardiological pathology among the population. In northern regions heavy climate, low temperatures and small duration of light day complicate the situation. Difficult geographical conditions can negatively influence on epidemiological situation in

districts (figure1) [4].

The main in structure cardiovascular nosologies are circulatory system diseases. Indicators in Kamchatka Krai till 2016 remain higher in comparison with Russian and Far East. The tendency to their decrease can be explained with implementation of federal and regional target programs, medical examination of the population, promoting of a healthy lifestyle, improvement of diagnostics and treatment.

The Arterial Hypertension (AH) is one of the most widespread chronic diseases. Around the world, researches on optimization of therapy are actively conducted [14]. According to the last recommendations of the European Society of Cardiology, the target level of the arterial blood

pressure (BP) has to be reached no later than in 3 months after an initiation of treatment. At the same time less than 50% of the patients receiving antihypertensive therapy reach the level of systolic BP<140 mmHg. It proves relevance of a problem of increase in compliance of patients. One of the easiest ways of growth of this is use of the multicomponent drugs. In the recommendations of 2018 the class and level of validity of initiation of therapy from the double fixed-dose combination is raised to IB. There are recommended combinations of inhibitors of – angiotensin-converting-enzyme inhibitor (ACE inhibitor) or the angiotensin II antagonists to blockers (ARA) with calcium channel blockers of a dihydropyridine structure (AC) or thia-



zide diuretic (D), it is preferable in «one tablet» (IA) [2].

In the Russian Federation researches of features of a current of AH [1,6,9] are also actively conducted. The recommendations of the All-Russian scientific organization of cardiologists and the Russian Medical Society of Arterial Hypertension [12] are revised. The combinations of ACE inhibitors+AC/D [5,8,10,11,13] are the most studied. Advantages of use of combinations of ACE inhibitors and  $\beta$ -blockers ( $\beta$  – AB) [7], three-component antihypertensive drugs are analyzed [3].

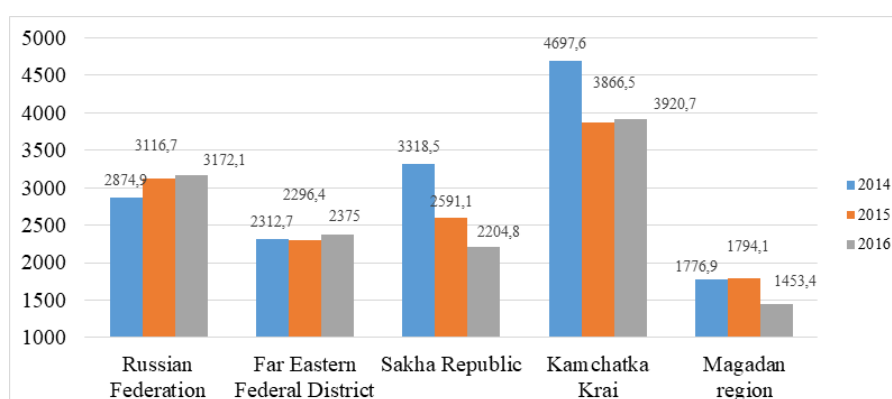
The analysis of the pharmaceutical market is one of the most reliable ways of assessment of introduction of the existing regulations in real clinical practice and also usage by patients of antihypertensive medicines. The **purpose** of the conducted research: comparison of approaches to drugs therapy of AH with use of the fixed-doses combinations in three northern regions of the FEFD.

**Material and methods.** The epidemiological research was conducted based on data on realization of antihypertensive medicines in the pharmaceutical organizations (n=17) during 2013-2017 in the Magadan region, in Kamchatka Krai, in the Sakha Republic (Yakutia). Based on the obtained data the general base of sales in a quantity equivalent (by the number of packing's) has been carried out with use of Microsoft Office of Excel 2015. Injection medicines, in connection with their use, generally in a hospital segment have been excluded from the list. At the following study phase the total indicators of sales of the established daily doses (DDD) all international non-proprietary name (INN), were calculated on the basis of DDD, presented on the website of World Health Organization. In the analysis of the fixed-doses combinations, the rule is followed: 1 tablet - DDD for the combinations applied once a day; 2 tablets - DDD for the combinations applied twice a day and 3 tablets DDD for the combinations applied three times a day, etc. This principle means what the DDD of fixed-doses combination can differ from the DDD of its active ingredients [15]. Further the average indicator of realization of each INN in the specific region on 1 drugstore sold for a year (for alignment of differences of population density in regions) was calculated. The "Analysis of Data" and "Intermediate Results" package was used.

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**Compliance to the principles of ethics:** research work conforms to the ethi-



**Fig.1.** Indicators of incidence of circulatory system diseases on 100000 all population of northern subjects of the FEFD (with the diagnosis established for the first time in life)

cal standards developed according to the Helsinki declaration of the World medical association "Ethical Principles for Medical Research Involving Human Subjects" with amendments of 2000. The epidemiological research was conducted without participation of people and animals.

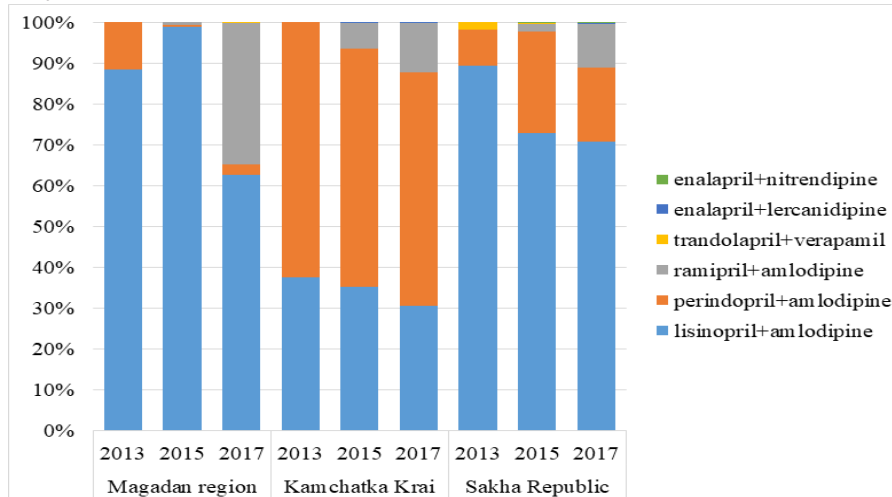
**Acknowledgements:** none.

**Results and discussion.** In a therapeutic class of combinations  $\beta$ -AB+AC/D more than 90% of realized amount by DDD were from the leader - an atenolol with chlortalidone in all three analyzed districts. Only in 2017 the share of sales bisoprolol+amlodipine in the Sakha Republic (Yakutia) has increased to 11,11%. Indicators of acquisition of INN bisoprolol+hydrochlorothiazide in Yakutia and the Magadan region were less than 3%. Patients in northern regions of the FEFD did not demand combinations atenolol + amlodipine, metoprolol + felodipine, nebivolol + amlodipine for the studied period. The narrow list of the fixed-doses combinations acquired by patients characterizes therapeutic group of the ARA+AC. The leader of the market is the combination valsartan+amlodipine. More than 95% of an intra-group indicator of realization are the share of this INN. Only since 2017, losartan+amlodipine

and telmisartan+amlodipine have begun to be applied by patients in Kamchatka Krai and in the Sakha Republic (Yakutia). At the same time, totally their share has made less than 5%.

Changes that are important in the data of sales were observed in a therapeutic class of combinations the ARA+D. More than 80% of realization intra-group remains the leader - INN losartan+hydrochlorothiazide. Since 2017 patients buy combination INN valsartan+hydrochlorothiazide were: in the Magadan region - 4,8%; in Kamchatka Krai - 7,8%; in the Sakha Republic (Yakutia) - 11,02%. Shares of sales kandesartan/telmisartan+hydrochlorothiazide in the Magadan region have increased to 3,4% in 2017, and combinations azilsartan medoxomil+chlortalidone to 12,18% in the Sakha Republic (Yakutia).

The therapeutic group of combinations of ACE inhibitors+AC is one of the most demanded in the pharmaceutical market in regions. The structure of realization of these fixed combinations for the studied period in three districts is presented in the figure 2. In the Magadan region more than 50% of intra-group volume acquired by DDD were the share of a combination of lisinopril with amlodipine, and sales



**Fig.2.** Structure of realization of the DDD fixed-doses combinations ACE inhibitors+AC

of perindopril+amlodipine decreased. In 2017 was increased to 35% the indicator of sales of rather new fixed-doses combination ramipril+amlodipine and has occurred come a redistribution of preferences. The share of this INN in the Sakha Republic (Yakutia) in 2017 has made more than 10%. In general, the structure of realization in regions was similar. At the same time, patients in Sakha Republic (Yakutia) actively bought the fixed combinations of a perindopril+amlodipine. Their share has made about 25% in 2016 and 18% in 2017.

Preferences of experts and patients in Kamchatka Krai differed from the regions described above. The leader of the therapeutic group of ACE inhibitors+AC was perindopril+amlodipine. More than 50% of sales were the share of this INN in the district. Since 2015 there is a market redistribution - realization of a combination lisinopril+amlodipine decreases to 30% in favor of INN ramipril+amlodipine – his indicator increases to 10%. Combinations of trandolapril+verapamil and also rather new drugs, which containing enalapril+lercanidipine and enalapril+nitrendipine, were not demanded among patients in regions. In general, decrease in demand for drugs of an enalapril is noted. It can be connected with feature of pharmacokinetics of the substance (applied twice a day). It reduces at patients commitment to treatment, while there are effective, long acting ACE inhibitors (perindopril, ramipril, fosinopril) in the market.

Dynamics of realization of the fixed doses combinations in the ACE inhibitors+D group is presented in the figure 3. The leader was the combination perindopril+indapamide. The share of its sales varied from 20% (in 2015 in the Magadan region) up to 60% (in 2017 in Kamchatka Krai). Indicators of sales of INN enalapril+indapamide were insignificant (no more than 10%) and decreased in three studied districts. Use by patients of a combination enalapril+hydrochlorothiazide was also decreased in the Magadan region and in Kamchatka Krai. Shares of other representatives of this therapeutic class remained insignificant - totally no more than 10%. The increase in realization was also observed for combinations of ramipril+hydrochlorothiazide and lisinopril+hydrochlorothiazide in the Sakha Republic (Yakutia).

At the following study phase the sales of the fixed-doses combinations of drugs from various therapeutic classes have been analysed. Dynamics of realization is presented in the figure 4. In the Magadan region the most acquired there were combinations hydrochlorothiazide+triamterene

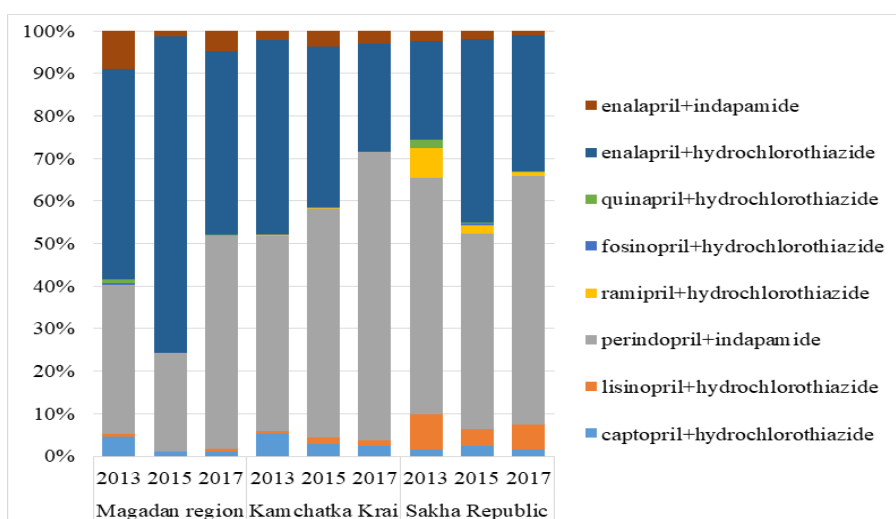


Fig.3. Structure of realization of the DDD fixed-doses combinations ACE inhibitors+D

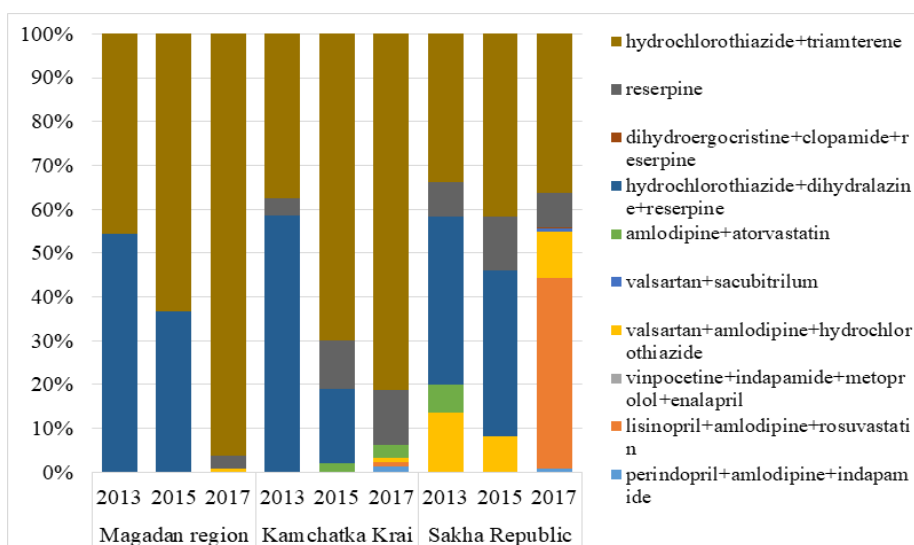


Fig.4. Structure of realization of the DDD fixed-doses combinations of antihypertensive drugs of other therapeutic classes

and hydrochlorothiazide+dihydralazine+reserpine. Despite emergence of modern multicomponent medicines ACE inhibitors+AC+D, ACE inhibitors+AC+statins, the ARA+ AC+D, AC+D, AC+statins, ACE inhibitors+D+ $\beta$ -AB+nootropic in the pharmaceutical market, their total share made no more than 10%. The situation in Kamchatka Krai was similar, but at the same time, high rates (over 60% intragroup in 2013 year) characterized sales of alkaloids of a *Rauwolfia serpentina* (trade name "Rau-natine").

The pharmaceutical market of the Sakha Republic (Yakutia) also differed in view of considerable acquisition of combinations of a reserpine with hydrochlorothiazide. At the same time, market redistribution nevertheless happened, and an intra-group share of a combination lisinopril+amlodipine+rosuvastatin by 2017 has made more than 40%. At INN valsartan+amlodipine+hydrochlorothiazide indica-

tors of sales have increased to 10%.

Despite existence in the pharmaceutical market of combinations of more selective  $\beta$ -AB (bisoprolol, metoprolol, nebivolol), till 2017 year the most acquired by patients there is an atenolol combination. It can be explained with the accumulated experience of its clinical application, presence duration in the regional pharmaceutical markets and also rather low cost of the concrete trade name «Tenorik».

The significant proportion of realization of INN valsartan+amlodipine among combinations of the ARA+AC can be caused by recent registration and, respectively the entry to the regional pharmaceutical markets, trade names of combinations of an irbesartan, losartan, olmesartan medoxomil and telmisartan with amlodipine. Till 2017 in drugstores this group has been presented, generally by the trade name «Exforge».

In the therapeutic class ARA+D redistribution of preferences from a com-

bination of a losartan with hydrochlorothiazide, in favor of rather new INN was observed. Current situation can be a consequence of increase in interest of specialists and patients to group of sartans in general, an active promotion, acquisition of practical experience of use of medicines by doctors and patients in northern regions of the FEFD.

In group of the fixed-doses combinations ACE inhibitors+AC remained high a share of realization lisinopril+amlodipine. It can be caused by the fact that this combination was one of the first in the regional pharmaceutical markets. Nevertheless, entry of new options of combinations has attracted interest of specialists. This can be connected with a later registration (only in 2015 year) of a full-doses combination «Ekvator» (20 mg +10mg), and also the increase in number of researches devoted to efficiency and safety of a combination perindopril+amlodipine [5,8,10,11,13]. The lack of sales of INN enalapril+nitrendipine/lercanidipine can be explained with recent registration of medicines (2016-2017) and need of accumulation of practical experience of usage in the form of single component drugs.

In a therapeutic class of combinations of ACE inhibitors+D considerable and stable share of sales at a perindopril+indapamide what can be explained with synergism of action due to vasodilating properties, additional at diuretic. Decrease in demand for combinations of enalapril can be caused by registration and entry into the pharmaceutical market of combinations of a ramipril, a fosinopril and quinapril and also growth of interest in combinations of ACE inhibitors+AC and ARA+D and ARA+AC.

Traditional preference of acquisitions by patients of combinations of diuretics and medicines with reserpine shows need of informing doctors about new double-component, triple-component drugs, effective for treatment of patients with an arterial hypertension, according to National clinical guideline (2018).

**Conclusion.** In general sales of antihypertensive combinations are characterized by concentration around several INN. The most realized fixed combinations in northern districts of the FEFD are atenolol+chlortalidone, valsartan+amlodipine, losartan+hydrochlorothiazide, lisinopril+amlodipine, perindopril+amlodipine, perindopril+indapamide. Leaders of therapeutic groups can vary considerably depending on the specific regions of the FEFD. Despite registration and availability in drugstores of regions of modern multicomponent drugs, acquisition by patients of medicines of a reserpine in

2013-2017 years and insignificant usage of the drugs containing three and/or four active ingredients, except for the Sakha Republic (Yakutia), still takes place. Results of a research prove slow introduction of recommendations in real practice of the antihypertensive therapy, which is appointed to patients, in the remote northern regions of the Russian Federation. The structure and dynamics of development of the pharmaceutical market shows need actions for expansion of knowledge of doctors about new standards of therapy, about the registered multicomponent drugs with the fixed-doses, which allow increasing compliance of patients to the appointed treatment.

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## ASSOCIATION OF ACE GENE POLYMORPHISM WITH HYPERTENSION AND RISK FACTORS AMONG INDIGENOUS PEOPLE OF THE NORTHERN TERRITORY OF YAKUTIA

DOI 10.25789/YMJ.2018.64.29

#### ABSTRACT

A study of the association of insertion-deletion (ID) polymorphism of the ACE gene with arterial hypertension and risk factors of cardiovascular diseases in the indigenous people of the northern territory of Yakutia was conducted. The obtained data show that the representatives of the indigenous population with the ID genotype of the ACE gene are associated with a level of systolic blood pressure, abdominal obesity. Carriers of this genotype of the ACE gene have the greatest chance of developing hypertension, metabolic syndrome. The heterozygous DD genotype is associated with lipid metabolic disorders both in hypertensive patients and persons without hypertension. Therefore, the research confirms influence of the D allele ACE gene polymorphism onto genetic mechanisms of cardiovascular diseases development.

**Keywords:** polymorphism, ACE gene, arterial hypertension, indigenous people, risk factors.

**Introduction.** Hypertension (HTN) is one of the main cardiovascular disease risk factors and the main reason for a high mortality among adult population in

the world [3, 6]. The prevalence of HTN is rather high in the world: it is on the average by 22% among adult population, according to WHO data [16]. Rising of

arterial blood pressure is a multifactorial disease which development is defined by the difficult mechanism of interaction of genetic and not genetic risk factors and

influences of the environment [9, 14]. For today it is proved that the genetic contribution can be considered main in development of HTN. In this process the important role belongs to the genes coding the components of the renin-angiotensin system (RAS), especially to the angiotensin-converting enzyme (ACE) [11- 13]. Previously, many researches confirmed the influence of D allele of the ACE gene on the development of an idiopathic hypertension, abdominal obesity and the chronic coronary artery disease [5, 10]. There was a research where the association of ACE gene ID polymorphism with a myocardial infarction in men (Yakuts up to 50 years) was revealed [1]. The research of association of ACE gene polymorphism with hypertension among indigenous people of arctic territories of Russia is insufficiently studied and remains relevant.

**Research objective** – studying of association of ACE gene polymorphism with hypertension and risk factors among indigenous people of the northern territory of Yakutia.

**Materials and methods of the research.** The clinico-epidemiological study of indigenous people in remote districts in the North of Yakutia is conducted: in Kolymskoye and Andryushkino rural localities of the Nizhnekolymsky District, Topolinoe rural locality of the Tomponsky District, Nelemnoye rural locality of the Verkhnekolymsky District. 348 people were examined using the continuous method. Patient sample consisted of adult population aged from 20 up to 70 years, 225 women, and 123 men. The response made 75%. Average age of the respondents was 45,71±0,67 years, of women 47,4±0,836 of men 42,6±1,09 years.

Inclusion criteria: representatives of indigenous people of Yakutia (Evens, Chukchi, Yukaghirs, Yakuts).

Exclusion criteria: representatives of non-indigenous nationality.

The program of the research includes the following sections: the questionnaire poll for assessment of an objective state; the informed consent of a respondent to carrying out researches, blood donation (according to the Ethical Committee Protocol); anthropometric examination with measurement of waist circumference, thigh size; blood sampling from basilic vein in the morning on an empty stomach with 12-hour continence from nutrition. Blood drawing for the molecular genetic testing was carried out from a median cubital vein to a test tube with EDTA. Genomic DNA allocated from leucocytes of a peripheral blood with phenol-chlo-

roform extraction technique [Maniatise-tal. 1982]. Genotyping of ID polymorphic marker of ACE gene was carried out by means of sets (LLC NPF Litekh, Moscow) according to the manufacturing company instruction on Real-time CFX96 amplifier ("BioRad", the USA).

Laboratory methods of the research included blood lipids test (TC, TG, HDL Cholesterol, LDL Cholesterol), glucose test.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the V revision of Society of cardiology of Russian Federation (VNOK), 2012, into account the European recommendations, 2011. Hypercholesterolemia (HCS) is the level of total cholesterol (TC)  $\geq 5,0$  mmol/l, the high LDL Cholesterol level  $>3,0$  mmol/l, the low HDL Cholesterol level  $<1,0$  mmol/l in men;  $<1,2$  mmol/l in women, the hypertriglyceridemia (HTG) is the TG level is  $\geq 1,7$  mmol/l; a hyperglycemia on an empty stomach (a glucose in a blood plasma on an empty stomach  $\geq 6,1$  mmol/l) or glucose intolerance (a glucose in a blood plasma in 2 hours after glucose loading within  $\geq 7,8$  and  $\leq 11,1$  mmol/l).

The measurement of blood pressure was carried out according to the standard procedure World Health Organization/ International Organization of Hypertension (1999). Hypertension is present at the 140/90 mmHg (The Russian references developed by Committee of experts of VNOK, 2004, 2009).

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM)  $\geq 80$  cm on women,  $\geq 94$  cm on men.

The study was conducted according to Ethics Committee protocol YSC CMP on the respondent's informed consent to the processing of personal data and the study.

Statistical data processing was carried out by means of standard methods of mathematical statistics, using the software package of SPSS (version 17.0). Data are submitted as  $M \pm m$  where  $M$  – average value of the sign size, and  $m$  – an average error of the sign size. Intergroup differences were estimated by means of the variance analysis or nonparametric criteria. When comparing frequencies of genotypes the standard criterion  $\chi^2$  with Yeats's amendment was used. The relative risk (RR) of a disease with a certain genotype was calculated by a standard formula  $OP = a/bxd/c$  where  $a$  and  $b$  – the number of the patients having and not having a mutant genotype respectively, and  $d$ ,  $c$  – a number of people in the con-

trol group, having and not having a mutant genotype. RR had a 95% confidence interval. The differences were considered as statistically significant at  $p < 0,05$ .

The research was conducted within research projects of YSC CMP "A contribution of a metabolic syndrome to development of atherosclerosis of coronary arteries in residents of Yakutia", R & D "Development of new technologies of treatment and risk prediction of hypertension and insult in the Republic of Sakha (Yakutia)" (Government contract No. 1133).

**Results of researches and discussion.** In the general population distribution of genotype frequencies is shown in table 1. As you see, ACE gene ID genotype (65,2%) is the most frequent. The groups were created for the research: the persons having arterial hypertension (175 people), and the group of control – the persons without HTN (173 people). Average age of hypertensive patients was 53,11±0,51 years, the persons without HTN – 38,88±0,60 years.

Results of the comparative analysis of distribution of allele frequencies and genotypes in groups of hypertensive patients

Table 1

PDistribution of genotype frequencies of a polymorphic site ID ACE gene

Genotype	Frequency	%
II	68	19,5
ID	227	65,2
DD	53	15,2

Table 2

Distribution of allele frequencies and genotypes of a polymorphic site ID ACE gene in groups of hypertensive patients and control

Allele frequencies and genotypes		Patients	Control
I	N	186	177
	%	53.1	51.2
	$\chi^2(P)$ ; OP (95% ДИ)	0.20 (0.6536) 1.08 (0.80-1.47)	
D	N	164	169
	%	46.9	46.8
	$\chi^2(P)$ ; OP (95% ДИ)	0.20 (0.6536) 0.92 (0.68-1.26)	
I/I	N	35	33
	%	20	19.1
	$\chi^2(P)$ ; OP (95% ДИ)	0.01 (0.9343) 1.06 (0.60-1.86)	
I/D	N	116	111
	%	66.3	64.2
	$\chi^2(P)$ ; OP (95% ДИ)	0.09 (0.6774) 1.10 (0.69-1.75)	
D/D	N	24	29
	%	13.7	16.8
	$\chi^2(P)$ ; OP (95% ДИ)	0.44 (0.5058) 0.78 (0.42-1.47)	

Table 3

Mean concentrations of lipid spectrum and glucose among hypertensive patients and control group depending on ID genotypes of ACE gene

Blood parameters	Genotype II		Genotype ID		Genotype DD		p
	with HTN	without HTN	with HTN	without HTN	with HTN	without HTN	
TC	5.05±0.14	4.68±0.16	5.15±0.09*	4.79±0.07*	5.13±0.16	4.71±0.16	*0.004
LDL CS	3.24±0.13	2.88±0.13	3.32±0.08*	3.05±0.06*	3.32±0.14	3.07±0.12	*0.008
HDL CS	1.26±0.05	1.37±0.06	1.26±0.03	1.33±0.03	1.28±0.06	1.14±0.05	
TG	1.21±0.09#	0.92±0.07#	1.21±0.05*	0.91±0.03*	1.16±0.10	1.07±0.08	*0.000 #0.023
Glucose	4.48±0.18	4.41±0.14	5.02±0.17*	4.19±0.08*	4.48±0.27	4.25±0.14	*0.000

and control didn't show statistically significant differences (Tab. 2). We carried out the comparison of average concentration of fats and glucose in the carriers of this or that genotype of ACE gene. By comparison of TC average values, significant differences between the carriers of ID genotype and DD genotype ( $4.97 \pm 0.06$ ,  $4.91 \pm 0.12$ , respectively,  $p=0.000$ ) and ID and II ( $4.97 \pm 0.06$ ,  $4.87 \pm 0.11$ ,  $p=0.000$ ) are identified.

Comparing the median concentration of LDL Cholesterol, it is taped that carriers of the genotype II had reliable differences in comparison with the genotypes ID and DD ( $II - 3.07 \pm 0.09$ ,  $ID - 3.19 \pm 0.05$ ,  $DD - 3.18 \pm 0.09$ ,  $p=0.000$ ). Also, there were the differences in comparative analysis of median values of HDL Cholesterol ( $II - 1.31 \pm 0.04$ ;  $ID - 1.29 \pm 0.02$ ;  $DD - 1.20 \pm 0.04$ ,  $p=0.000$ ). Statistically significant differences in Tg median values between the compared groups were among the DD genotype carriers in comparison with two others ( $DD - 1.11 \pm 0.06$ ;  $II - 1.07 \pm 0.06$ ;  $ID - 1.07 \pm 0.03$ , respectively,  $p=0.000$ ). By comparison of median values of glucose, the significant differences isn't identified ( $II - 4.45 \pm 0.11$ ;  $ID - 4.62 \pm 0.10$ ;  $DD - 4.36 \pm 0.11$ ,  $p>0.05$ ).

In the general population, frequency of hypercholesterolemia is 51,5% in carriers of II homozygous genotype, 42,7% in carriers of ID heterozygous genotype, and 49,1% in carriers of DD heterozygous genotype; the differences were doubtful. Frequency of atherogenic LDL hypercholesterolemia was significantly higher in carriers of DD genotype (64,2%), in comparison with carriers of genotypes II and ID (54,4 and 54,6% respectively). The frequency of Hypo-alpha-cholesterolemia among the compared groups of the significant differences are not identified ( $II - 33,8\%$ ,  $ID - 34,8\%$ ,  $DD - 35,8\%$ ,  $p>0.05$ ). Also, there were not the significant differences of TSH in carriers of dif-

ferent genotypes ( $II - 11,8\%$ ,  $ID - 11,9\%$ ,  $DD - 11,3\%$ ,  $p>0.05$ ). The greatest frequency of hyperglycemia is identified in ID genotype carriers - 6,6%, and, in comparison with other genotypes, has significant difference ( $II - 2,9\%$ ,  $p=0.035$  and  $DD - 3,8\%$ ,  $p=0.13$ ).

Furthermore, we carried out the comparison of fats and glucose median values among carriers of genotypes II, ID, DD separately in the groups of hypertensive patient and control.

By comparison of median concentration of fats and carbohydrate spectrum in persons with HTN and in the group of control, the significant differences were identified only in carriers of genotypes ID: TC ( $5.15 \pm 0.09$  and  $4.79 \pm 0.07$  respectively,  $p=0.004$ ), LDL Cholesterol ( $3.32 \pm 0.08$ ,  $3.05 \pm 0.06$ ,  $p=0.008$ ), Tg ( $1.21 \pm 0.05$ ,  $0.91 \pm 0.03$ ;  $p=0.000$ ), blood glucose ( $5.02 \pm 0.17$ ;  $4.19 \pm 0.08$ ,  $p=0.000$ ), except the HDL Cholesterol ( $1.26 \pm 0.03$ ;  $1.33 \pm 0.03$ ,  $p>0.05$ ). The significant differences of TC median values were not identified in homozygous carriers of genotypes II ( $5.05 \pm 0.14$ ;  $4.68 \pm 0.16$ , respectively,  $p>0.05$ ), and in comparing LDL Cholesterol ( $3.24 \pm 0.13$ ;  $2.88 \pm 0.13$ , respectively,  $p>0.05$ ), HDL Cholesterol ( $1.26 \pm 0.05$ ;  $1.37 \pm 0.06$ ,  $p>0.05$ ), Tg ( $1.21 \pm 0.09$ ,  $0.92 \pm 0.07$ ;  $p>0.05$ ), glucose ( $4.48 \pm 0.18$ ;  $4.41 \pm 0.14$ ,  $p>0.05$ ). The comparisons between groups of DD car-

riers also did not reveal the significant differences: TC ( $5.13 \pm 0.16$ ,  $4.71 \pm 0.16$ ,  $p>0.05$ ), LDL Cholesterol ( $3.32 \pm 0.14$ ;  $3.07 \pm 0.12$ ,  $p>0.05$ ), HDL Cholesterol ( $1.28 \pm 0.06$ ;  $1.14 \pm 0.05$ ,  $p>0.05$ ), Tg ( $1.16 \pm 0.10$ ,  $1.07 \pm 0.08$ ;  $p>0.05$ ), glucose ( $4.48 \pm 0.27$ ;  $4.25 \pm 0.14$ ,  $p>0.05$ ).

We carried out the assessment of frequency of lipid and metabolism disorders separately among hypertensive patients and persons without HTN. Hypertensive patients have the largest frequency of hypercholesterolemia (66,7%) (Fig. 1), atherogenic hypercholesterolemia (70,8%) - in persons with DD genotype. The most frequent hypo-alpha-cholesterolemia and hyperglycemia are identified in heterozygous carriers, and HTG - in II homozygous carriers. Differences between them did not reach statistically significant values.

In the control group, the largest frequency of hypercholesterolemia is identified in the group of II genotype carriers (42,4%) (fig. 2). Atherogenic hypercholesterolemia was high in all persons without HTN, DD homozygous carriers had the highest frequency of atherogenic hypercholesterolemia (58,6%). There is the same situation with the frequency of hypo-alpha-cholesterolemia (44,8%). Thus, the influence of DD genotype on lipid storage disease is revealed.

Also, we surveyed the association of

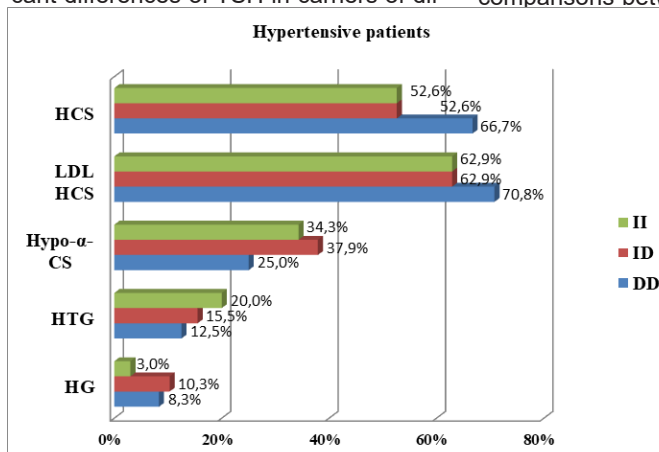


Fig.1. Frequency of lipid and metabolism disorders separately depending on the genotype ACE gene among hypertensive patients

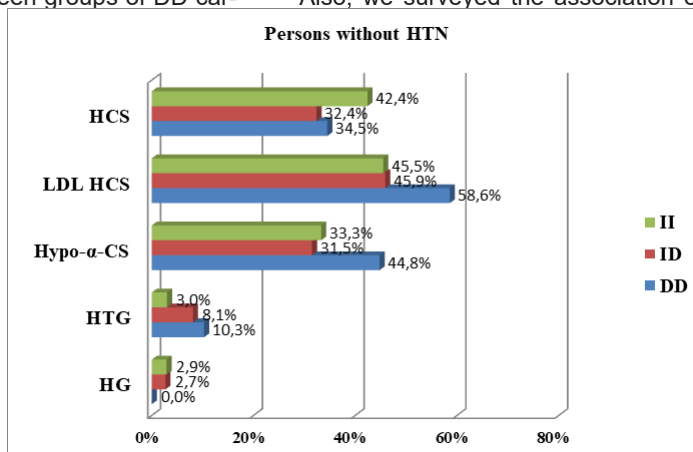


Fig.2. Frequency of lipid and metabolism disorders separately depending on the genotype ACE gene among persons without HTN



ACE genotypes with the level of the systolic blood pressure. The average level of systolic blood pressure in carriers of ID heterozygous genotype ( $144,2 \pm 1,2$  mmHg) was significantly higher in comparison with the carriers of homozygous genotypes II and DD ( $136,6 \pm 2,8$  and  $138,8 \pm 2,1$  mmHg., respectively,  $p=0,02$ ).

Abdominal Obesity is independent risk factor of metabolic syndrome and cardiovascular diseases. We defined associativity of genotypes to the average waist measurement (WM) and AO. By comparison the average WM, we received significant differences between ID genotype carriers and carriers of other genotypes ( $OT_{ID}=89,61 \pm 0,65$ ,  $OT_{II}=86,46 \pm 1,49$ ,  $OT_{DD}=86,75$ ;  $p<0,05$ ). There are statistically significant differences in the frequency of AO between ID carriers (59,9%) and II and DD carriers (55,9%, 50,9%).

We compared WM separately in groups with HTN and without HTN. It is shown that, among persons with HTN, significant differences are in carriers of genotype ID ( $WM=96,23 \pm 0,89$ ) comparing with II homozygous carriers ( $OT=91,43 \pm 1,99$ ,  $p=0,033$ ), DD ( $OT=92,63 \pm 1,27$ ,  $p=0,022$ ). Among persons without HTN there are no significant differences: ID -  $82,68 \pm 0,68$ , II -  $81,18 \pm 1,85$ , DD -  $81,90 \pm 1,21$ . In general, hypertensive patients had a high frequency of AO. Among genotypes the highest frequency of AO is in ID genotype - 84,5%. It statistically differed from DD - 66,7% ( $p=0,001$ ), and didn't differ from II - 71,4%. Frequency of AO in persons without HTN among carriers of this or that genotype had no significant differences; it varied within II - 39,4%, ID - 34,2%, DD - 37,9%.

**Conclusion.** The obtained data show that representatives of indigenous people of the North of Yakutia with ID genotype of ACE gene, abdominal obesity is associated with the level of systolic arterial blood pressure. Thus, carriers of this genotype have the highest probability of idiopathic hypertension, metabolic syndrome. It is also confirmed by the researchers conducted by some foreign authors [4, 7, 8, 15]. The DD heterozygous genotype is connected with lipid storage disease, both in hypertensive patients, and persons without hypertension.

Therefore, the research confirms influence the D allele ACE gene polymorphism onto genetic mechanisms of cardiovascular diseases development. Data

are compounded with references of foreign researchers [2, 5, 10].

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## SCIENTIFIC REVIEWS AND LECTURES

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## DIAGNOSTIC SIGNIFICANCE OF THE HUMAN PAPILLOMA VIRUS DETECTION IN BLOOD

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### ABSTRACT

There is still no clear understanding of the human papillomavirus infecting, as well as its eliminating process from the body. It is known that cervical cancer is caused by human papillomavirus in 99 percent of cases, but only in a small number of human papillomavirus infected women leads to develop cervical cancer. At the same time, based on cytological and histological analysis of the women cervical samples, it is currently impossible to establish criteria that would indicate the malignant progression possibility. Blood, as a unique tissue with specific and nonspecific protective adaptive mechanisms, can be a source of crucial information about the human body papillomavirus infecting. The article provides an overview of the research devoted to the human papillomavirus detection in blood and identifies unresolved issues arising from these studies.

**Keywords:** papillomavirus, HPV, blood, viremia.

Human papillomaviruses (HPV) are small double-stranded DNA viruses that infect epithelial cells. Approximately one third of them have tropism to the genital epithelium. These viruses can be divided into high-risk types (including HPV-16, -18, -31 and -33), which are associated with the development of anogenital malignant neoplasms and low-risk viruses (including HPV-6 and -11) that induce hyperproliferative lesions, but they are associated with malignant neoplasms rarely [24]. Types 16 and 18 are responsible for most cases of cancer caused by human papillomaviruses [26].

In the case of cervical cancer, HPV is the causative agent in about 99 % of incidents [20]. It is widely known that only in a small number of women infecting HPV leads to the development of invasive cancer. It is not yet possible to establish reliably the based on cytological and histological tests criteria that indicate the progression of pathological changes to cervical cancer [31].

Until nowadays, we have not clear understanding the cellular immune response mechanisms that contribute to the HPV elimination [23]. The innate immunity, including macrophages, natural killer T-cells is thought to play a crucial role in the first line of defense against HPV infection [27].

Insufficient knowledge of the HPV-infecting and HPV-eliminating expands the field of investigations. The research clarifying blood significance in these processes is of particular interest.

It is supported for a long time that HPV does not cause viremia. Previously, HPV DNA found in blood was interpreted as DNA from metastatic tumor cells [4].

Over time, due to molecular biology improvement, evidence has emerged of the HPV presence in the blood of patients with malignant tumors, pre-carcinogenic changes, and in healthy people. Instead, previously, blood in healthy people was

considered to be sterile [12].

To date, the HPV genes presence in the blood has been shown in a significant number of studies.

Peripheral blood mononuclear cells (PBMCs) from women with cervical cancer detected HPV types 16 and 18 genes [10], women with asymptomatic urogenital HPV infection - genes 6, 11, 16, 18 [22], HIV-infected pediatric patients (median of age 13.2 years) - HPV-16 genes [4]; men with infected HPV-16 sperm - HPV genes of the same type [21]. PBMCs of healthy blood donors, it was also possible to detect the HPV-16 genes [4]. In Australia, from healthy blood men donors from PBMC, many various genes of HPV types belonging to the skin beta and gamma papillomaviruses, alpha papillomavirus mucous were identified. Here-with high-risk HPV genes were found in 1.7% of cases. It is shown that HPV is attached to the cell surface, not inside [15]. Evidence of HPV reproduction in the PBMCs is currently absent.

In the serum, HPV-16 and 18 genes were found from patients with cervical cancer [25, 3], rectal cancer, oropharyngeal cancer [3], and squamous cell head and neck cancer [6]. HPV-16 DNA was found in the serum of patients with breast cancer [11, 5], as well as with benign breast neoplasms [5].

In plasma from patients with cervical cancer, DNA of HPV 16 and 18 types [7,1,16], 45, 51, 52 types [16] was determined. From patients with asymptomatic cervix infection in the plasma, DNA of HPV 45, 51, 16 types was detected, and HPV-16 showed the highest viral load [17].

In cord blood HPV types 6, 11, 18, 52 DNA was detected [30].

In whole heparinized blood HPV 16 and 18 type genes were found from patients with cervical cancer [9] and lung cancer [29].

Data on the HPV type matches in the

blood and in the cervix is different. Some researchers found that the HPV type in the cervix and in the blood is the same [14,9], in other studies it was shown that the HPV type may not coincide [17,8].

The results of studies on the correlation between the HPV DNA presence in the blood and the cancer starting prognosis are contradictory as well. Some studies suggest that HPV DNA detection in blood samples may be a useful severity marker of the diseases associated with HPV, metastasis, or recurrence [7, 6, 17, 18, 19]. However, Peedicayil et al. showed that detection of HPV DNA in plasma is not a prognostic marker for cervical cancer recurrence [2].

Many notions remain without a clear explanation, including how HPV enters the blood, whether viremia is a natural stage of HPV infecting, and how blood participates in the HPV eliminating.

Being the oldest human companions, HPV is considered by researchers as a source for exploring evolutionary several million year history [13]. To achieve such evolutionarily successful lifestyle, HPV must avoid host protection systems through immune evasion [28].

In other turn, the human body connected with HPV in over million years, ought to develop efficient physiological mechanisms that contribute to the virus removal.

**Conclusion.** The high potential of blood as a unique tissue that unites the whole body and possessing specific and nonspecific protective and adaptive mechanisms, determines the continuing considerable interest in scientific research.

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## NECESSITY OF SCREENING PATIENTS WITH STENTING FOR ACUTE CORONARY SYNDROME BY CYP2C19 POLYMORPHISM

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#### ABSTRACT

The *relevance* of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

One of the main drugs for antiplatelet therapy in cardiology is clopidogrel, the use of which can reduce the incidence of thrombotic complications. Clopidogrel is the most famous member of the thienopyridine group. Clopidogrel remains the main drug for antiplatelet therapy in patients who received stenting of the coronary vessels for acute coronary syndrome. The rationale and design of the observational study aimed at testing the hypothesis that the high frequency of the genetic polymorphism of cytochrome CYP2C19\*2 is associated with coronary stent thrombosis is presented.

**Keywords:** Clopidogrel, coronary stenting, the acute coronary syndrome, personalized therapy, clopidogrel resistance, paradoxical response, genetic polymorphisms.

The relevance of this article is due to the fact that cardiovascular diseases are currently the leading cause of death and disability worldwide. The leading role in the structure of mortality from cardiovascular diseases belongs to coronary heart disease. Ischemic heart disease (IHD) is a chronic disease that develops with insufficient oxygen supply to the myocardium. The main cause (more than 90% of cases) of insufficient intake of oxygen is the formation of atherosclerotic plaques in the lumen of the coronary arteries, the arteries of the blood supplying the heart muscle (myocardium).

According to the World Health Organization (WHO), mortality from cardiovascular disease is 31% and is the most common cause of death worldwide. In the territory of the Russian Federation, this figure is 57.1%, of which the share

of CHD falls more than half of all cases (28.9%), which in absolute terms is 385.6 people per 100 thousand people per year. For comparison, mortality from the same cause in the European Union is 95.9 people per 100 thousand people a year, which is 4 times less than in our country. The incidence of IHD increases dramatically with age: in women from 0.1-1% at the age of 45-54 to 10-15% at the age of 65-74 years, and in men with 2-5% at the age of 45-54 years to 10-20% at the age of 65-74 years. Despite the multiply increased possibilities of modern conservative therapy of the above pathology, in the absence of effect, surgical methods of treatment are performed:

1. Percutaneous coronary intervention - balloon angioplasty with the installation of a stent (a metal frame that preserves the restored lumen of the vessel);

2. Coronary bypass - the imposition of shunts around the affected areas of the coronary arteries. As a shunt, one uses his own veins (usually the subcutaneous vein of the thigh) or the internal thoracic artery of the patient.

Percutaneous coronary intervention (PCI) is one of the widely used methods for treating patients with acute coronary syndrome. In the Russian Federation, in 2012 the number of PCI increased by 13,049 procedures or 20.9%, compared to 2011, and amounted to 75,378 procedures. The average for Russia, indicator of the frequency of PCI performance per 1 million population in 2012 was 531 [3]. It is important to note that, despite the obvious success of the use of PCI, this method has certain complications. Thus, among patients who underwent coronary stenting, the frequency of such a

life-threatening complication as acute or subacute stent thrombosis, according to international literature, reaches 1-3% [2]. In this case, the frequency of repeated interventions on a stented coronary vessel can reach 17% (especially when implanting a stent without drug coating) [3]. In order to reduce the risk of developing cardiovascular disasters, the patient needs to use antiplatelet drugs after performing PCI and stenting of the coronary vessels.

One of the main drugs for antiplatelet therapy in cardiology is clopidogrel, the use of which can reduce the incidence of thrombotic complications. Clopidogrel is the most famous member of the thienopyridine group. It like ticlopidine and prasugrel, refers to prodrugs. The drug has a complex metabolism. Its absorption in the intestine and entry into the blood is associated with the P-glycoprotein encoded by the MDR1 gene (ABCB1). 85% of the dose is converted into an inactive carboxyl derivative due to the action of esterase plasma. The remaining 15% of the dose undergoes two-stage oxidation under the action of cytochrome P450 isoforms, first turning into 2-oxo-clopidogrel, and then into the active thiol derivative. In turn of it irreversibly inhibits the binding of ADP to the P2Y<sub>12</sub>-receptor platelets. Further, inhibition of fibrinogen binding to the GP IIb / IIIa receptor and reduction of aggregation occurs. Clopidogrel is used in patients with acute coronary syndrome (ACS), including those who underwent coronary artery stenting (SCS) with percutaneous coronary intervention (PCI) [4]. The standard route of administration of clopidogrel provides a loading dose of 300 mg and then a maintenance dose of 75 mg daily; the increased dosage includes the administration of 600 mg in a loading dose, then 150 mg for 6 days and thereafter 75 mg per day [23] or a maintenance dose of 150 mg per day for 6 months. [25]. Double antiplatelet therapy is often used, involving the simultaneous use of clopidogrel and acetylsalicylic acid preparations, both for long-term treatment and for short periods (1 month after PCI with stenting) [25], although it has now been shown that the use of clopidogrel without combination with aspirin is associated with a significant reduction in hemorrhagic complications without an increase in the frequency of thrombotic events [26].

In recent years, significant progress has been made in the development of new inhibitors of the receptor for ADP P2Y<sub>12</sub> (prasugrel, ticagrelor) with a faster onset of action, more pronounced platelet inhibition, and possibly a better efficacy profile than clopidogrel used in the standard dosage, but clopidogrel

remains the first-line drug due to significant differences in the availability of innovative P2Y<sub>12</sub> inhibitors in European countries. Antiplatelet therapy to optimize the results of SCS should provide a balance between the minimized risk of stent thrombosis and the risk of bleeding [17].

At the present time, it has become evident that the systems of conveyors and biotransformation have genetic polymorphism, characterized by the presence of enzyme isoforms with high and low activity. Accordingly, there are genetic characteristics that affect the pharmacological response in a particular patient. Depending on the status of this gene, three groups of individuals are distinguished: homozygotes (without mutations), heterozygotes (mutation in the 1st allele), persons with a mutant genotype (mutations in two alleles). Based on the genotype CYP2C19, three main phenotypes of the metabolizer CYP2C19 can be distinguished: \*1/\*1 - "fast" with normal functional activity of the enzyme, \*1/\*2 - "slowed" with reduced enzyme activity, \*2/\*2 - "slow" - significantly reduced by the functional activity of the enzyme or its absence. The so-called wild type of the CYP2C19 gene (\*1st allele) is characterized by normal enzymatic activity of CYP2C19. The most common allelic variant of CYP2C19 with loss of function is the allele \*2. The frequency of genotypes according to CYP2C19, corresponding to slow metabolizers in the Russian population, is 11.4%, which is comparable to European ethnic groups. However, in Russian patients with ischemic heart disease (IHD), CYP2C19 genotypes associated with slow metabolism can occur at a frequency of up to 27.3% [6]. Cytochrome CYP2C19 is a member of the cytochrome P450 family of enzymes and is an S-mefenitronine hydroxylase enzyme. Low enzyme activity is associated with a risk of developing myocardial infarction or ischemic stroke - in patients with decreased enzyme activity, the risk of death from cardiovascular events increased by 53%. The gene encoding cytochrome CYP2C19 is located in 10 chromosomes, locus 10q24. This locus is part of a large cluster containing the genes CYP2C19, CYP2C18, CYP2C19, CYP2C9, CYP2C8, and associated with a reduced response to clopidogrel based on the results of a full-genome assay of associations [7].

The allelic variant CYP2C19\*2 (rs4244285) refers to prothrombogenic variants of cytochrome CYP2C19. Replacement G < A (Gly681Ala) is associated with high residual platelet aggregation after taking clopidogrel, increased thrombogenesis and a general deterioration

in the prognosis in patients with cardiovascular pathology, especially after stent placement. This applies to homozygotes A/A (\*2/\*2), carriers of this genotype belong to the group of slow metabolizers, but patients with heterozygotes G/A (\*1/\*2) are also characterized by a reduced rate of clopidogrel metabolism. Currently, the possibility of administering large doses of clopidogrel to such patients is being discussed, but no unambiguous recommendations have yet been developed.

After the introduction of PCI with stenting from the 1980s, the rate of restenosis was 24%, then after improving the intervention procedures and introducing more advanced stent models, the incidence of restenosis decreased to 1-2%. However, according to Russian studies, in our country this situation remains disappointing, since the recurrence of ACS due to stent thrombosis develops on average in 8% of patients. In connection with the development and massive introduction of these high-tech methods of treatment of cardiovascular diseases in our country and in our region, the question of increasing the number of patients with genetically determined resistance to the so-called "standard scheme" of disaggregant therapy: aspirin (75 mg) + clopidogrel (75 mg) due to the polymorphism of CYP2C19, an increase in the complications in the form of restorations of implanted stents. It has been demonstrated that the addition of clopidogrel to ASA provides additional benefit in patients with MI, especially with coronary artery stenting. At the same time, in a number of studies, a wide interindividual variability of the antiplatelet effect of clopidogrel has been demonstrated. Pharmacodynamic and clinical studies have demonstrated that the polymorphism of the CYP2C19 gene (CYP2C19\*2 allele) is associated with a decreased antiplatelet effect of clopidogrel and an increase in the incidence of severe cardiovascular complications [8]. Evidence of a thorough analysis of the effectiveness of clopidogrel is published in the leading cardiological journals of the world, debates in European and American cardiology forums. Various components of the effectiveness of clopidogrel - compliance, dosages, duration of two-component antiplatelet therapy, the effect of concomitant treatment with statins, proton pump inhibitors, and the effects of other factors (smoking) are discussed.

The contribution of the polymorphism of the CYP2C19 gene to the formation of the phenomenon of resistance to clopidogrel has been confirmed by numerous studies. Thus, a randomized ISAR study refers to carriage of the \*2 CYP2C19

allele with an independent predictor of stent thrombosis within 30 days. A triple increase in the risk of stent thrombosis in patients with acute coronary syndrome (ACS) and the presence of the CYP2C19\*2 allele was also shown by the TRITON-TIMI study [25]. A study performed on a Chinese population found an increased risk of occurrence of cardiovascular complications within 1 year after PCI of 3.65-fold in the carrier group of at least one mutant CYP2C19 allele (\*2 or \*3) compared to the wild-type genotype [22]. A meta-analysis of nine studies, which included 9685 patients, showed a statistically significantly higher risk of death for cardiac and vascular reasons, as well as stent thrombosis in patients who are "slow metabolizers" compared to individuals who do not have alleles with a reduced functional activity [20]. In the PAPI (Pharmacogenomics of Antiplatelet Intervention) study, clopidogrel was administered within 7 days to 429 healthy individuals; the response was determined by the method of aggregometry. Genotyping of CYP2C19\*2 was performed. Data obtained from healthy individuals were compared with the data of 227 patients undergoing stenting of the coronary arteries. We studied the relationship between platelet function, genotyping and cardiovascular outcomes. It was found that the response to clopidogrel was highly dependent on heredity ( $p < 0.001$ ): 13 single-nucleotide polymorphisms in the chromosome 10q24 in the CYP2C18-CYP2C19-CYP2C9-CYP2C8 cluster were significantly associated with a reduced response to clopidogrel. Patients with the CYP2C19\*2 allele had more MTB or fatal outcomes during the year (20.9% versus 10.0%, risk ratio 2.42,  $p = 0.02$ ) [24].

In a meta-analysis conducted by M.V.Holmes, with the inclusion of 32 studies totaling 42,000 respondents, the genotype influenced only the incidence of stent thrombosis, in connection with other cardiovascular outcomes not demonstrated [15].

At the same time, the results of a large randomized PLATO study revealed the association of various polymorphic CYP2C19 markers with the incidence of cardiovascular events in patients with ACS only in the early stages of the disease, after a year of observation, the differences were not significant. The results of large studies [16, 18, 20] confirmed the prognostic value of the polymorphism of the gene CYP2C19 in patients taking clopidogrel. In a meta-analysis of 9 pharmacogenetic studies of clopidogrel that included 9685 patients, a reliable association was found between homo- or heterozygotes for a mutant allele with a

decreased function of CYP2C19 and an increased risk of cardiovascular death, myocardial infarction, or cerebral stroke [11].

A domestic study conducted in 2015 also confirmed the association between the carriage of CYP2C19\*2 in patients after PCI and the risk of developing resistance (due to high residual platelet activity) [5].

The accumulated knowledge served as the basis for introducing in 2010 the instructions on the use of original clopidogrel information on the effect of the mutant gene CYP2C19 on the effectiveness of therapy. The American Heart Association and the American Society of Cardiology, the European Society of Cardiology, note the need for genotyping for CYP2C19 to detect alleles of "slow metabolizers" and recommend it for some groups of patients at high risk of thrombotic complications, mainly with ACS and planned PCI. The carrier frequency of the CYP2C19\*2 allele in the Russian population is about 13.3%, and in the IHD patients this is slightly higher (the incidence of genotypes with reduced metabolic activity may reach 27.3%) [13].

In our country, there is also growing interest in this issue, in connection with which in various clinics, patient studies are conducted. So in 2013, a study was conducted at the National Medical Science Centre of Cardiovascular surgery named after A.N.Bakulev with the participation of 72 patients (50 men and 22 women) who took clopidogrel after the operation of planned myocardial revascularization performed a genetic study on the carriage of allelic variants of cytochrome P-450 and CYP2C19\*1 and \*2 isoenzymes. As a result, it was concluded that the carriage of allelic variants of the CYP2C19\*2 gene according to different authors is found in the population with a frequency of up to 40% (confirmed by the results of the study) and is one of the risk factors for low laboratory response to clopidogrel therapy [4]. Carrying out the genetic test for carriage of CYP2C19\*2 to all patients before stenting can help optimize the appointment of antiplatelet therapy, which in turn could prevent the potential complications associated with insufficient effectiveness of clopidogrel.

Summing up, there is a need for further larger-scale research in this area, the purpose of which will be to develop new clinical guidelines for the treatment of cardiovascular patients, which ultimately aims to increase life expectancy.

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## EXPERIENCE EXCHANGE

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# HOSPITAL MORBIDITY RATES AS A FACTOR IN THE SELECTION OF PATHOLOGY TO DEVELOP PERSONALIZED PREVENTION AND TREATMENT METHODS

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## ABSTRACT

Indicators of the hospitalized incidence of adult population according to YSC CMP Hospital during 2015-2017 are presented in article. The characteristic of dynamics and structure of the cases demanding performing treatment in stationary conditions is given. Growth of cases of hospitalization of patients with metabolic disorders, including diabetes 2 types and diseases of cardiovascular system is established. The obtained data served as the basis for conducting research and developing molecular genetic methods of diagnosis in relation to this pathology.

**Keywords:** hospital morbidity, structure and dynamics of incidence, methods of personalized medicine, molecular diagnostics.

**Introduction.** Diseases with the inheritance of predispositions today are widespread and are determined by a factor called the genetic load. It is the high prevalence of polymorphic variants of genes predisposing to the development of multifactorial diseases that determines the spectrum of somatic pathology with a characteristic for a specific population structure. In addition, the polymorphism of variants of predisposing genes affects not only the structure, but also the characteristics of the formation and course of diseases, the development of complications, as well as the susceptibility, resistance and tolerance of drug therapy [4].

Today, molecular technologies allow the formation of risk groups taking into account the genetic characteristics of patients and carrying out preventive measures in them at the stage of preclinical manifestations of the disease in order to prevent the development of the disease itself and its complications. Personalized medicine methods are highly effective and contribute to improving the quality and increasing the life expectancy of the population. In turn, the use of such expensive and highly specific technologies requires an informed approach to the choice of both the spectrum of diseases and genetic markers that predispose to the development of pathology.

To determine the significance of a particular pathology helps a comprehensive assessment of public health, which is carried out using indicators of general and primary morbidity recorded by attendance, as well as using data on morbidity

with temporary and permanent disability, morbidity from the results of medical examinations and hospitalization activity of the population [3].

As a factor in the selection of pathology by degree of importance, such an indicator of medical statistics as hospitalized morbidity is often used, which gives an idea of the most severe pathology requiring attention and treatment in inpatient conditions, as a rule, in specialized departments. This indicator is very informative, since it characterizes neglect and severity of pathology, which in turn contributes to the formation of a chronic process and disability, which ultimately leads to a decrease in the patient's quality of life [1].

The unit of accounting for hospitalized morbidity is the case of hospitalization of the patient in the hospital, and the accounting document is the "Statistical map of the out-of-hospital" (f. 066 / u). The "statistical card of the discharged from the hospital" is compiled on the basis of the "Medical card of the inpatient patient" (f. 003 / u) and is a statistical document containing information about the disused, discharged from the hospital (discharged, dead). The card is compiled simultaneously with the recording of the epicrisis in the "Medical card of the inpatient" by the attending physician on all those who left the hospital (written out or died). The card reflects the basic information: about the duration of treatment of the patient in the hospital, the diagnosis of the main and concomitant diseases, the duration, nature and effectiveness of surgical care,

the outcome of the disease, etc. from which the patient has left. In cases where two or more diagnoses of diseases are indicated in the map, the patient refers to each of these diseases in the report, which was the main cause of hospitalization. This document provides the most rational development of information for the preparation of the relevant sections of the report [3,5]. Thus, the **purpose** of this study is to study the dynamics and structure of the hospitalized morbidity of the adult population of the RS (Ya) according to the data of the YSC CMP Hospital as a factor in selecting the most significant pathology for determining the priority directions of molecular genetics research in the development of diagnostic test systems for multifactorial diseases.

**Materials and methods.** The base of the study was the Yakut Science Centre CMP (Yakutsk), the object being the adult population from 18 to 80 years old, hospitalized in the hospital in 2015–2017. The material for analyzing the dynamics and structure of the hospitalized morbidity was the data from the statistical reports of the inpatient units of the Hospital of the Yakutsk Scientific Medical Center. The statistical data processing was carried out using descriptive statistics methods.

**Results and discussion.** In its structure, the Hospital of the YSC CMP has 110 beds of which 44 are therapeutic, 41 are cardiological and 25 are gynecological. To identify current trends in the dynamics of hospital morbidity, a preliminary analysis of the organization of inpatient care was carried out. Accord-

ing to the official statistics of the Hospital YSC CMP in 2015, the hospital incidence rate was 2.256; in 2016 - 3.025; in 2017 - 2,984. Thus, over the 3-year period, the hospitalization rate increased 1.3 times (Table 1).

According to the results of the analysis, it was established that over the past three years there has been an increase in cases requiring patients to be hospitalized with endocrine pathology, eating disorders and metabolic disorders by 4.2 times, including type 2 diabetes, there is a tendency to a steady increase in the hospitalization of diseases of the circulatory system, for three years, this figure increased by 304 cases. At the same time, for some diseases, there is a tendency to reduce the level of hospitalization, so the number of cases requiring hospitalization of neoplasms decreased by 3.6 times, which may be due to timely diagnosis, treatment in the early stages of cancer (Table 2).

The table shows that in the general structure of the diseases, among all those admitted for the 3-year period, patients with circulatory system diseases prevailed (46.0%; 45.2%; 45.2%); second place (15.7%; 16.4%; 17.2%) and in third place were cases related to the pathology of the urogenital system (11.9%; 10.0%; 9.6%).

**Conclusion.** The paper describes the characteristics of the dynamics and structure of the hospitalized morbidity of the adult population of the RS (Ya) on the basis of a retrospective analysis of data from statistical reports of inpatient wards of the YSC CMP Hospital.

It is established that for the period from 2015 to 2017 there is a tendency of a steady increase in the incidence of cases requiring hospitalization for patients with endocrine pathology, eating disorders, metabolic disorders, as well as patients with circulatory disorders. The data obtained indicate the activation of metabolic disorders among the adult population of RS (Ya) receiving medical care at the YSC CMP Hospital and require a more detailed analysis of the pathogenesis mechanisms of the formation of this group of diseases using molecular diagnostic methods, the development and implementation of which will facilitate the implementation of personalized preventive and therapeutic measures that will reduce the risk of development and complications of these diseases. Taking into account the results obtained by the staff of the Laboratory of Hereditary and Population Genetics of the YSC CMP, together with the doctors of the therapeutic department of the YSC CMP Hospital,

**Table 1**  
The relative number of diseases that caused the hospitalization of the population in the inpatient hospital of the YSC CMP Hospital for 2015-2017 by disease class

Class of international classification of diseases X revision	2015	2016	2017
	Per 1000 population		
I. Some infectious and parasitic diseases	0.005	0.037	0.024
II. Neoplasms	0.047	0.027	0.011
III. Diseases of the blood, blood-forming organs and certain disorders involving the immune mechanism	0.024	0.053	0.048
IV. Endocrine, nutritional and metabolic diseases	0.046	0.181	0.258
V. Mental and behavioral disorders	0.003	0	0
VI. Diseases of the nervous system	0.079	0.109	0.103
IX. Diseases of the circulatory system	1.061	1.387	1.365
X. Respiratory diseases	0.117	0.123	0.109
XI. Diseases of the digestive organs	0.132	0.128	0.111
XII. Diseases of the skin and subcutaneous tissue	0.013	0.015	0.009
XIII. Diseases of the musculoskeletal system and connective tissue	0.114	0.160	0.140
XIV. Diseases of the genitourinary system	0.274	0.305	0.288
XV. Pregnancy, childbirth and the postpartum period	0.361	0.500	0.518

**Table 2**  
The overall structure of the disease hospitalized cases in the YSC CMP Hospital for 2015-2017

Class of international classification of diseases X revision	2015	2016	2017
	%		
I. Some infectious and parasitic diseases	0.3	1.3	0.9
II. Neoplasms	2.2	1.0	0.6
III. Diseases of the blood, blood-forming organs and certain disorders involving the immune mechanism	1.2	1.9	1.8
IV. Endocrine, nutritional and metabolic diseases	2.1	6.1	8.9
V. Mental and behavioral disorders	0.4	0	0
VI. Diseases of the nervous system	3.5	3.7	3.1
IX. Diseases of the circulatory system	46.0	45.2	45.2
X. Respiratory diseases	5.3	4.2	3.7
XI. Diseases of the digestive organs	5.8	4.3	3.9
XII. Diseases of the skin and subcutaneous tissue	0.6	0.6	0.4
XIII. Diseases of the musculoskeletal system and connective tissue	5.0	5.3	4.7
XIV. Diseases of the genitourinary system	11.9	10.0	9.6
XV. Pregnancy, childbirth and the postpartum period	15.7	16.4	17.2

research is currently being conducted to study the molecular genetics aspects of the formation of metabolic disorders such as type 2 diabetes, obesity, and non-alcoholic fatty disease liver, hypertensive disease.

*The research protocol was approved by the local committee on biomedical ethics at the YSC CMP. The work is carried out in the framework of the research "Study of the genetic structure and burden of hereditary pathology of populations of the Republic of Sakha (Yakutia)".*

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## THE MOST FREQUENT SYMPTOMS OF JOINTS DAMAGE AMONG THE RESIDENTS OF YAKUTIA

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#### ABSTRACT

The frequency of clinical manifestations in patients with joint damage among the indigenous people of Yakutia (n = 687) was studied. It is revealed that the damage of the joints can begin both in the early childhood (2 years) and in old age (77 years); on average, joint lesion starts at 41-43 years.

The most common symptoms of joint damage are pain in the joint and crepitus in the knee joints. Among women, there are more often observed: swelling of the wrist and knee joints, restriction of mobility of the wrist joints and bilateral crepitus at the knee joints; among men, one-sided crepitus at the knee joints. With age increasing, the duration of pain and the frequency of changes in the configuration of the joints at the time of inspection increase.

**Keywords:** joint damage, clinical symptoms, radiological signs.

**Introduction.** Data on the prevalence of diseases of the joints abroad in many cases are based on the results of screening tests. The pathology of the joints in this method revealed in 10.3-35.8% of [5, 6]. Russian researchers have shown that there are geographic variations in the prevalence of pain in the joints. Thus, during a screening questionnaire in Krasnoyarsk region did not exceed 15% [1]. Yuzhno-Sakhalinsk complaints of pain imposed on 21% of the population in the joints [3], and they met in 36.5% of cases [2] among the rural population of the Sverdlovsk region. The high prevalence of arthralgia was established in the Republic of Sakha (Yakutia) - up 46.7%, that perhaps due to the influence of climatic factors [4]. It was extremely high frequency of pain in the joints among industrial workers Republic of Karelia, where the figure approached 65%. Moreover arthralgias appearance was not dependent on the severity of physical activity, and apparently was due to other factors.

Purpose of the study - to study the

frequency of symptoms of joint damage among rural residents of Yakutia.

#### Material and methods of research.

687 patients were examined, revealed during a continuous epidemiological study rural residents of the seven villages in Yakutia. Of these, 68.1% were females, 31.9% - male. The median age of men and women was about the same - 50 and 49 years respectively. The minimum age for both sexes was 18 years old; the maximum age of the men was 88 years, women - 80. The age structure of the largest part consisted of persons in age group 40-49 years - 32.9% (including women - 23.4, men - 9.5); 27.2% were persons aged 50-59 years (including women - 19.5, men - 7.7). Persons of other age groups accounted for no more than 15%. Sex ratio was not significantly different in age groups ( $p > 0.05$ ).

**Results and discussion.** The most common joint disease among both women and men began at the age of 40-49 years - 40.2 and 27.8%, respectively. Among the 23.7% of men and 23.5%

women the damage of the joints began at the age of 30-39 years. In other age groups the beginning defeat joint damage met not more than 20% of cases.

The most significant differences in the frequency the beginning defeat joint damage among both sexes were observed in the age group 40-49 years ( $\chi^2 = 17,46$ ;  $p = 0,03$ ;  $V = 0,16$ ).

We have also studied the frequency of clinical signs of joint damage. The study revealed that the most frequent clinical manifestations of joint disease are pain in the joints (100% of patients), and crepitus in knee joints (54%). With a frequency of 10 to 30% met: change in joint configurations (28.2%), one joint arthritis (25.1%) and swelling of knee (12.5%). In 3-10% of patients were observed: knee limited mobility (10%), swelling of the proximal interphalangeal joints (PIPhJ) brushes (6.4%), swelling of the wrist (4.6%), limiting the mobility of the hip joint (HJ) (3.9%), the wrist mobility restriction (3.6%), swelling of the hand metacarpophalangeal joints (MCPPhJ) (3.5%), arthritis of three

or more joints (3.3%) and symmetrical arthritis (3.2%). Positive rheumatoid factor (1.5%) and rheumatoid nodules (0.6%) occur most often.

Because radiological signs osteophytes most frequently (24.5%) and a narrowing of the articular slits (19.8%) occur most often.

At the analysis of the frequency of symptoms of gender, statistically significant differences were found in the frequency of the following four symptoms:

- 1) swelling of the wrist;
- 2) swelling of knee joints;
- 3) limitation of motion of the wrist;
- 4) crepitus in knee joint during active movements.

Swelling radiocarpal joints is more common among women than among men ( $\chi^2 = 7.09$ ;  $p = 0.03$ ). Swelling of wrist was often among women bilateral than unilateral (3.8% versus 2.1). Among men frequency wrist swelling on the one or on both sides it was similar (0.9%).

Swelling of the knee is also often observed among women than among men ( $\chi^2 = 7.45$ ;  $p = 0.02$ ). A bit more often knee swelling P among women was on one side than on the two (8.1% vs 6.4). Among men, by contrast, the frequency of swelling on both sides of the knee was more than one (5% vs. 3.2).

Bilateral limited wrist mobility was more common among women than among men (3.6% versus 0.5); unilateral - among women occurred in 1.5% of cases in men - were noted ( $\chi^2 = 13.3$ ;  $p = 0.001$ ).

Crepitus in the knee, both among women and among men was more often on both sides than the one (47.2% vs. 9.8% and 35.1 vs. 12.3, respectively). Bilateral crepitus in knee joints with active movements was more common among women (47.2% against 35.1 for men), whereas the one - most men (12.3% vs. 9.8 for women) ( $\chi^2 = 8.95$ ;  $p = 0.01$ ) (fig.8).

When analyzing the frequency of symptoms depending on the age group, statistically significant differences were found in the frequency of two symptoms: duration of pain and change in configuration of the joints at the time of inspection (fig.9).

The duration of pain was significantly dependent on the age of the studied ( $\chi^2 = 17.46$ ;  $p = 0.03$ ). At the age of 18-39 years in most cases, the pain lasted for up to 1 week in the 40-49 years - more than half a month and up to 1 week with the same frequency, after 50 years - more than half of the month. The frequency of pain lasting less than a week

with the increase of age was significantly decreased by 71.4% between the ages of 18-19 years to 0 at the age of 80-89 years ( $p = -0.98$ ;  $p < 0.001$ ). Frequency of pain lasting longer than half a month, in contrast, increased with an increase in age from 28.6% at age 18-19 years and 100 aged 80-89 years ( $p = 0.95$ ;  $p < 0.01$ ). Frequency of pain duration of 2 weeks of age was not significantly dependent ( $p = 0.05$ ;  $p > 0.05$ ) (Fig.2).

Changing of the joints configuration at the time of examination of statistically highly significant depended on the age group ( $\chi^2 = 68.58$ ;  $p < 0.00001$ ).

With increasing age, the frequency of changes in the joints configuration at the time of inspection was increased from 0% at the age of 18-19 years to 50% at age 80-89 years ( $p = 0.93$ ;  $p < 0.01$ ).

The highest frequency of configuration changes observed in the age of 60-69 years (51.5%).

**Conclusions.** Joint disease begins to manifest itself clinically in an average of 41-43 years, but can begin in early childhood (2 years) and old age (77 years).

The most common clinical manifestations are joint pain and crepitus in knee joints. Women are more frequently observed: swelling of the wrist and knee joints, limited mobility of the wrist and bilateral crepitus in knee joints; among men - sided crepitus in knee joints.

With age increasing, duration of pain and frequency of changes in the joints configuration increased at the time of inspection.

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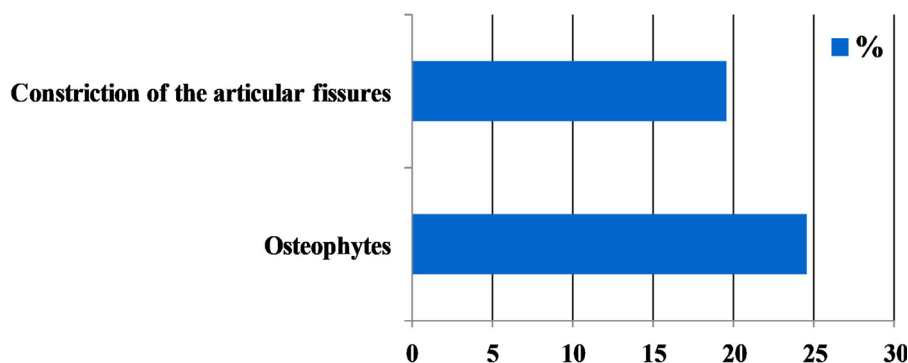


Fig.2. The frequency of radiological signs of joint damage

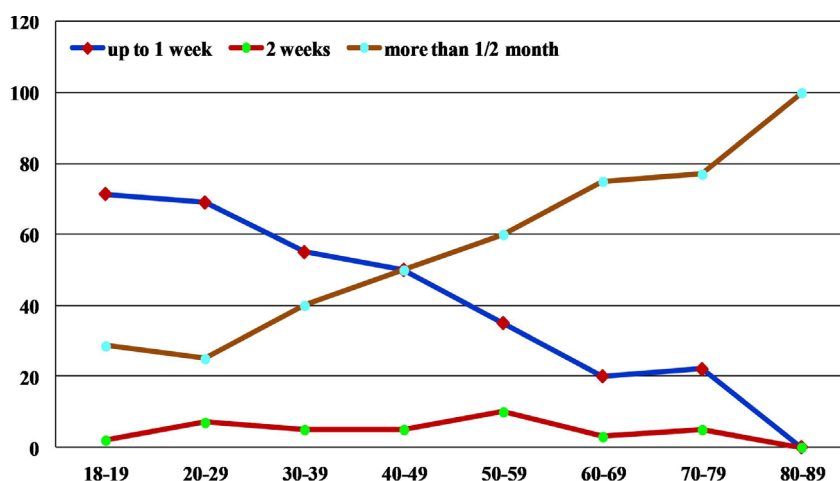


Fig.1. Duration of pain depending on age

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## METHODS OF DIAGNOSIS AND TREATMENT

### T. K. Davydova, T. Ya. Nikolaeva, Okoneshnikova L. T. COMPARATIVE ANALYSIS OF SPORADIC CASES AND FAMILY FORM OF PROGRESSIVE MUSCULAR ATROPHY OVER A 30-YEAR PERIOD (1986-2016) IN THE REPUBLIC SAKHA (YAKUTIA)

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#### ABSTRACT

Progressive muscle atrophy (PMA) is a rare disease of the motor neuron disease group (MND), which is characterized by selective lesions of the anterior horns of the spinal cord.

**Objective:** to study the features of the course of sporadic and family form of PMA over the period from 1986 to 2016.

**Materials and methods:** in 2006, a personalized register was introduced, which included patients with MND (amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar paralysis, primary lateral sclerosis). Since 1986 till 2006 patients were introduced after a retrospective study. The study included 15 patients with sporadic form and 5 patients from the same family. For the described study, patients with PMA were divided into 2 groups: 1 group included sporadic cases of progressive muscle atrophy (n=16), 2 group consisted of sick family members of a family case of 2 women and 2 men (n=4). Clinical examination of patients included assessment of somatic and neurological status in the onset of the disease and its further development, age of onset and duration of course.

**Research methods:** needle electromyography (EMG), Amyotrophic lateral Sclerosis Functional Rating Scale (ALSFRS) [9], spirometry (LNG), forced vital capacity (FVC), magnetic resonance imaging (MRI), computed tomography (CT) of brain and spinal cord. In 9 cases, direct DNA diagnosis was carried out to exclude Kennedy's Bulbo-spinal amyotrophy.

**Results:** Our study revealed a moderate rate of progression in sporadic cases and a slow rate of progression in the family form of PMA. In our study, the duration of PMA was significantly higher in the family form and was  $140 \pm 37.8$  and  $53.6 \pm 30.3$  months in sporadic cases ( $p = 0.003$ ). In the family form of the disease, an earlier age of debut was observed than in sporadic PMA and in men the disease began earlier than in women.

**Keywords:** motor neuron disease, amyotrophic lateral sclerosis, progressive bulbar paralysis, progressive muscular atrophy, primary lateral sclerosis.

**Introduction.** Progressive muscle atrophy (PMA) is a rare disease from the group of motor neuron diseases (MND), which is characterized by selective damage to the cells of the anterior horns of the spinal cord and manifests itself by progressive muscle weakness, hypotrophy and fasciculations. On the recommenda-

tion of the World Federation of Neurologists, since 1994 severe neurodegenerative diseases with unknown etiology and unspecified pathogenesis, characterized by selective damage of central and/or peripheral motor neurons, were referred to motor neuron diseases. For diseases in MND group a typical progressive course

with the same fatal outcome. This group includes amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), primary lateral sclerosis (PLS) and progressive bulbar palsy (PBP) [12].

The most common in the world disease in this group is ALS, which accounts for 80% in this group. The share



of PMA is 9%, PBP-8% PLS-2% [6]. For the first time, 11 patients with progressive muscular atrophy described in 1850 F. Aran [1]. In 1874 J. M. Charcot cited differences in the clinical and pathological picture of amyotrophic lateral sclerosis and progressive muscle atrophy and isolated ALS and PMA into separate syndromes. Considering the El-Escorial criteria adopted by the world Federation of Neurologists in 1990 and processed in 1998, PMA is not synonymous with ALS and is a separate nosological form [12]. In 1880 W. Osler described progressive muscle atrophy in 13 patients in two generations of the Farr family in Vermont; new cases of the same disease were described later by M. Brown, V. CudKowicz and co-authors who first reported that the disease in the Farr family was caused by a mutation of the A4V gene encoding cytosolic protein, the copper-zinc-dependent superoxide dismutase (CuZn-SOD) enzyme [1]. The A4V mutation is identified in approximately half of ALS familial cases associated with mutations of CuZn-SOD in the North America. This mutation is characterized by malignant, rapidly progressive course, and the life expectancy of patients rarely exceeds 2 years, averaging  $1.4 \pm 0.9$  years ( $n=84$ ). In addition, in patients with A4V mutation, both clinically and pathomorphologically interest of only peripheral motor neurons was revealed. In Yakutia, the disease is rare. In the MND group the share of PMA is 13%.

**Objective:** to study the peculiarities of sporadic cases and family form of progressive muscular atrophy in the Republic of Sakha (Yakutia)

**Materials and methods of the research.** In the Health Institute M.K. Ammosov NEFU on the basis of the neurological department of the Republican hospital № 2 – Center for emergency medical care (RH №2-CEMC) from 01.01.2006 a personalized register of patients with motor neuron disease is performed, which includes all patients with MDN, regardless of the form of the disease. In this register, retrospectively since 1986, after studying the medical documentation, according to El-Escorial criteria, patients with clinically significant ALS were included, and from 01.01.2006 with probable and possible ALS. In addition, patients with progressive bulbar paralysis, progressive muscle atrophy and primary lateral sclerosis were included. All of them were observed in the neurological Department of the RH №2-the CEMC of Yakutsk. A total of 154 patients were included in the regis-

ter as of 01.01.16, from which 124 were diagnosed with ALS (81%), 20 patients, including proband and sibs of the family case – PMA (13%), 4 patients - PBP (2.6%), 5 – PLS (3.3%).

For the described study, patients with PMA were divided into 2 groups: 1 group included sporadic cases of progressive muscle atrophy ( $n=16$ ), 2 group consisted of sick family members of a family case of 2 women and 2 men ( $n=4$ ).

Clinical examination of patients included assessment of somatic and neurological status in the onset of the disease and its further development, age of onset and duration of course. Needle electromyography was used to detect signs of damage to the PMN in acute and chronic denervation or denervation of the current-reinnervation process. Electrophysiological examination was carried out according to the Protocol of international recommendations for diagnosis of MND [10] to determine the rate of progression of the disease, the functional scale Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) was used [9]. The functional deficit was assessed by a 4-point system. At the same time, the loss of 9-12 points for 12 months was regarded as a rapid rate of progression, from 5-8 points, as an average rate of progression, from 0-4 points, as a slow rate of progression. Spirography (LNG) was carried out both in newly admitted patients and in re-admission. LNG was used to determine the volume of forced vital capacity of the lungs (FVC) and to identify the degree of progression of respiratory failure (RF). Reduction of FVC to 70-80% and below and reduction of FVC by 15% in 3 months was noted as a rapid progression of RF [5]. In addition, standard clinical and biochemical blood and urine tests were performed. Patients included in the register since 2006 magnetic resonance imaging and computed tomography of the brain and spinal cord were performed to exclude diseases with similar clinical manifestations with MND. In 9 cases, after the patients filled in the informed consent, direct DNA diagnostics was carried out to exclude Kennedy's Bulbo-spinal amyotrophy. The family anamnesis and the compilation of the pedigrees were carried out in the course of the conversation with the patient and his relatives.

**Results and discussion.** In general, the group of PMA patients included in the personalized register was 20 patients, including 5 women and 15 men. In the first group with sporadic form of PMA ( $n=16$ ) were 15 men and 1 woman. The second

group consisted of 4 patients ( $n=4$ ): a father and his children - 2 daughters and a son. Differential diagnostics was carried out as in sporadic cases and in a familial case: 1) hereditary Kennedy spinal-bulbar amyotrophy with X-linked recessive type of inheritance, which manifests itself in men in a relatively later age, usually after 40 years [8] and 2) genetically heterogeneous group of hereditary muscle diseases with similar phenotype of the disease - limb-girdle dystrophies (LGMD) 1A, LGMD 2A and LGMD 2N. For LGMD 1A typical dysarthria and dysphagia, may be present muscle weakness of the distal extremities; 2A LGMD, characterized by marked atrophy periscapular muscles, biceps, gluteal muscles, muscles of thighs; in LGMD 2N, possible late-onset and slower rate of progression [5]. The clinical picture in all the studied cases was typical for the phenotype of progressive muscular atrophy and was presented depending on the level of cerebrospinal axis lesions with flaccid paresis, amyotrophy, fasciculations, speech disorders, swallowing and phonation without sensitivity disorders, pelvic organ functions and cognitive impairment of Alzheimer's type. Needle EMG was performed in 15 cases (85%), in the remaining 5 cases EMG was not performed due to the severity of the patients. In all 15 cases, signs of anterior spinal cord injury were found. The absence of clinical symptoms of Central motor neuron lesion, as well as signs of neuronal denervation during needle EMG, as well as the absence of focal lesions on MRI and CT of the brain and spinal cord, characteristic of diseases with a similar clinical picture with ALS and PMA, allowed establishing the diagnosis of progressive muscle atrophy.

The age of onset of the disease in women with sporadic PMA was 57, 58 and 59 years, in men the average age was  $54.2 \pm 11.8$  years. With familial form of the disease, the age of debut for women was 40 and 50 years, men 38 years father 32 years and have a son. By the average age of debut in both groups the differences in student's T - test are statistically insignificant ( $p=0.06$ ). According to the Mann-Whitney test, statistically significant differences between the groups ( $p=0.003$ ) were revealed in the duration of the disease: in sporadic cases, the duration of the disease was significantly shorter than in the family case. The average duration of the disease in the group with sporadic disease was  $53.6 \pm 30.3$  months, and in the group with the family form of the disease  $140 \pm 37.8$  months.

By the place of residence urban resi-

dents - 5, rural - 14. According to ethnicity, 12 people are of the Yakut nationality, 8 - Russian. In the study of clinical symptoms in women (n=3), in the group of sporadic PMA in one case the disease began with weakness in the left thigh with further development of a sluggish lower paraplegia. In the second case - with weakness in the right hand and the development of brachial paraparesis and gradual generalization of the process, in the third - with distal paresis of the left leg and subsequent development of hemi- and tetraparesis. In men (n=13) in the group of sporadic PMA the disease began in 10 cases with weakness in a hand, which is then passed into the brachial diplegia and flaccid tetraparesis. In the remaining 3 cases, the disease manifested itself as a lumbar debut. In men, the family PMA disease (n=2) began with weight loss of the hands, tremors in them, fasciculations of the muscles of the trunk with a gradual involvement in the pathological process of the lower extremities and bulbar disorders at the end of life. Both in the last 2 years of life were bedridden, suffered from severe swallowing and speech disorders. The father died at the age of 52 years. The son, who died at the age of 46 years, bulbar disorders joined only 10 years after the onset of signs of the disease. The course of the pathological process was slowly progredient and was 14 years in each case. The eldest of the two sisters had symptoms of the disease at the age of 40 in the form of weakness in the legs: she had difficulty in climbing the stairs and the bus. Gradually joined the weakness in the hands, there were atrophy of the hands, feet, fascicular twitching and bulbar disorders. During the last 2 years of her life she was bedridden, unable to move, roll over in bed, had difficulty eating due to swallowing disorders. She died at the age of 48. The disease duration was 8 years. Younger sister (born in 1950) lives permanently in one of the CIS republics and periodically comes to relatives in Yakutia. She became ill at the age of 50. The illness started as well as an older sister with weakness in the legs, began to move slowly, with difficulty to climb stairs, could not hold the spoon, cup and other items. Atrophy of hands and feet, blurred speech appeared. Currently, the clinical picture of the disease in this patient is manifested by sluggish deep proximal tetraparesis, distal tetraplegia and moderate bulbar disorders, without pelvic and sensitive disorders. She moves in a wheelchair with assistance. The duration of her disease is currently 14 years. All members of the de-

scribed family belong to the Yakut ethnic group [2].

The cause of all deaths (n=18) is respiratory failure. 1 patient with a sporadic form of PMA was connected to the ventilator for 12 months. The duration of the disease was 38 months in this patient. According to the ALSFRS scale, the rate of progression in the family case was attributed to the slow type and amounted to the loss of functional activity from 2 - 4 points per year. In sporadic cases, the loss of functional activity was higher and amounted to 5-8 points per year, and the rate of progression was attributed to the average rate.

**Conclusions.** As a result of clinical observation, isolated lesion of peripheral motor neuron at different levels of the spinal cord was revealed in all 20 cases of MND. In this case, signs of involvement in the pathological process of the central motor neuron were not observed throughout the duration of the disease. Bulbar and respiratory disorders joined gradually as progression. The lethal outcome came from respiratory failure, due to aspiration pneumonia, paresis of the diaphragm muscles and auxiliary muscles involved in the act of breathing.

In general, the described cases of PMA are characterized by a moderate rate of progression in sporadic cases and a slow rate of progression in the family form of the disease. The obtained data correlate with the data of researchers from the United States [9], who compared the survival rate of patients with PMA and LAS on the example of 962 patients, of which 91 were with PMA and 871 with LAS. In the study, the survival rate of patients with PMA was significantly higher than that of patients with LAS. In our study, the duration of PMA was significantly higher in the family form and was  $140 \pm 37.8$  months against  $53.6 \pm 30.3$  months in sporadic cases of PMA ( $p=0.003$ ). Although at the familial form of the disease earlier age of debut was observed.

In the described family case of PMA, an autosomal dominant type of inheritance from a sick father was established for three of six children: proband and his two older sisters [3, 4]. In the clinical picture of the disease, attention is drawn to the relatively early debut of the disease in males 32 and 38 years and the onset of the disease from the distal upper extremities, while in women, the disease began later: in 40 and 50 years with weakness in the proximal lower extremities. In all cases, there is a slow progression of the disease.

Thus, both sporadic and hereditary

forms of PMA were registered in Yakutia, which are characterized by clinical polymorphism. Reported cases of PMA need further in-depth study using molecular-genetic and high-tech research methods. The results could help to reveal the immediate and probable causes of the etiology and pathogenesis of not only progressive muscle atrophy, but also other diseases of the group of motor neuron diseases.

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## PHARMACOLOGICAL AND SURGICAL TERMINATION OF MISSED ABORTION IN THE FIRST TRIMESTER AT THE DEPARTMENT OF GYNECOLOGY №1 OF THE SBI RS (YA) YAKUTSK CITY CLINICAL HOSPITAL

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### ABSTRACT

This article demonstrates the advantages of pharmacological medical termination of missed abortion. It presents an analysis of women's experiences of pharmacological and surgical terminal of missed abortion based on material from the Department of Gynecology №1 of the SBI RS (Ya) "Yakutsk City Clinical Hospital (YCCH)". The study included only patients with normal hemostatic system parameters. Patients with MA who have contraindications to the use of Mifepristone and Misoprostol were also not included in the group. The comparison group included 69 patients with MA, who underwent a surgical method of emptying the uterine cavity by vacuum aspiration. All patients were under observation in the gynecological department of the YCCH. To establish the diagnosis of MA a female pelvic ultrasound scan was performed using a vaginal sensor. The ultrasound control diagnosis was performed on the 14th day after taking Misoprostol and the vacuum aspiration.

The complications and treatment options are presented.

**Keywords:** embryo, anembryonic gestation, missed abortion, endometritis, pharmacological termination of missed abortion, vacuum aspiration, mifepristone, misoprostol, removal of embryo or fetus, hematometra.

**Introduction.** A missed abortion (MA), also known as a missed miscarriage or a silent miscarriage, is a pathology, in which for some reason the embryo (or fetus) ceases to develop and dies. The missed miscarriage takes a dominant position in the prevalence of reproductive losses. The incidence of MA is about 16-18% among pregnant women, and in the non-carrying prevalence of pregnancy, it reaches 45-88.6% of the number of spontaneous miscarriages at early stages. Endocrine dysfunctions, chromosomal abnormalities, different sexually transmitted infections, an insufficient amount of progesterone or an excess of androgens may lead to this pathology. Antiphospholipid syndrome can often be the cause of

embryonic death when clots form inside blood vessels. Moreover, the reasons for embryonic death could be toxic effects from radiation, alcohol and illegal drugs consumption, smoking. The International Federation of Gynecology and Obstetrics adopted a scientific consensus, according to which each case of MA is associated with chronic endometritis (XVIII FIGO Congress of Gynecology and Obstetrics: Kuala Lumpur, Malaysia, 2006). In chronic endometritis an endometrial lesion is accompanied by the development of receptor deficiency, the sensitivity of the mucous membrane of the uterus (endometrium) to steroids decreases, and the deficiency of cyclic transformations of the endometrium is marked. This may lead to

the disruption of implantation processes and, as a consequence, to MA.

In most cases the interruption of MA occurs independently, without any intervention in the uterine cavity, which reduces the risk of surgical, anesthetic, infectious inflammatory complications and reduces the psychogenic trauma for the patient [5]. Frequently, however, there is fetal egg retention and the question emerges about the most moderate way of eliminating it from the uterus. It has now been proven that the surgical method of emptying the uterine cavity during the MA is dangerous, since it facilitates to additional traumatization of the endometrium, which can complicate the achievement and the course of a subse-



quent pregnancy.

Consequently, according to current recommendations, it is necessary to use alternative options, the least traumatic of which is the pharmacological medical termination of MA. This method has several advantages: it does not require surgery and there is a natural restoration of the menstrual function after 28-30 days.

For the pharmacological termination of MA, antigestagens are used in combination with prostaglandins [1-3, 5]. The newest way to terminate pregnancy without surgery is the pharmacological (non-surgical) abortion, also known as a "velvet" abortion, by using Mifepristone. Mifepristone is a steroidal antiprogesterone. Mifepristone followed by a prostaglandin analog is the most typical method of medication used for medical abortion recommended by WHO. By blocking the action of progesterone, mifepristone alters the endometrium (the uterine lining), induces bleeding, and causes the uterine lining to shed. Mifepristone is used in conjunction with misoprostol. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents. If necessary, misoprostol can be repeated after 3 hours. This is the most effective and safe combination of medicaments [4]. In the absence of pharmaceutical effect, according to actual positions, vacuum aspiration is required, which has advantages over curettage in terms of safety [3].

Mifepristone must be taken in the presence of the prescribing physician. The Mifepristone pill should be 200 mg. The medication is then followed with 400 to 800 micrograms of misoprostol 36-48 hours later and must be taken in the presence of the doctor. Several to fifteen days later, the patient confirms that the abortion is complete. Medical ultrasound will confirm the completion. If the abortion is not complete, the clinician will perform a vacuum aspiration to empty the uterus.

**Purpose of the study:** to conduct a retrospective comparative analysis of pharmacological and surgical termination in the case of missed abortion at the first trimester of pregnancy, to identify the causes and evaluate the incidence of complications.

**Materials and methods of the research.** There has been conducted the analysis of pharmacological and surgical termination of missed abortion in a period of up to 12 weeks of gestation in 576 patients who applied to the gynecological department of the Yakutsk City Clinical Hospital in 2017.

507 women in whom the pregnancy was interrupted with the help of pharmacological agents composed the main group. One reason why patients might not use Mifepristone and Misoprostol for the purpose of interrupting MA was the risk of coagulopathic bleeding [2]. The study included only patients with normal hemostatic system parameters. Patients with MA who have contraindications to the use of Mifepristone and Misoprostol were also not included in the group. The comparison group included 69 patients with MA, who underwent a surgical method of emptying the uterine cavity by vacuum aspiration. All patients were under observation in the gynecological department of the YCCH. To establish the diagnosis of MA a female pelvic ultrasound scan was performed using a vaginal sensor. The ultrasound control diagnosis was performed on the 14th day after taking Misoprostol and the vacuum aspiration.

**Results and discussion.** Of 576 patients with MA in 486 (84%) cases the pregnancy proceeded according to the type embryonic death, in 90 (16%) by the type of anembryonic gestation.

544 pregnant women (94%) are residents of the city, 32 (6%) are from the village. By nationality, the Yakuts predominated being 369 (64%) patients, 127 are Russians (22%), 80 from other nationalities (14%).

The age of patients in the main group ranged from 18 to 41 years with an average value of  $28 \pm 6.5$  years and corresponded to the indicators in the comparison group. Of bad habits, smoking predominated, being 78%, and this is 396 pregnant women of the main group, and 75% - 52 patients of the comparison group. The number of female pelvic inflammatory diseases in the anamnesis, such as salpingoophoritis, chronic endometritis, cervicitis in both groups did not differ significantly and consisted of 242 patients - 42%. For 235 patients, with a missed miscarriage in the anamnesis, early spontaneous miscarriages followed by dilation and curettage and abortion, was 47%.

The patients hospitalized by pharmacological termination of MA at a period of 6-8 weeks of gestation were 321 (64%), with a period of 9-10 weeks, were 111 (21%), for 10-12 weeks, were 86 (15%). Surgical method of termination of MA was applied in 48 pregnant women with a period of 7-8 weeks, which was 70%, with a period of 9-10 weeks of gestation in 18 patients was 25%, with a period of 11-12 weeks 3 - 5%. In the main group

of patients who received Mifepristone at a dose of 200 mg, there were minor side effects in the form of nausea, headache for 21 (4%) pregnant women.

The embryo expulsion after taking Misoprostol in 306 patients (61%) occurred within 4-6 hours, with a gestation period of 6-9 weeks; after 2 days in 66 patients (13%), for the remaining 135 (27%) pregnant women after 3-4 days. An additional dose of the drug was required in 5 cases (5%).

For the patients of the main group, after medical cleaning of the uterus cavity, complications occurred in 31 (6%) cases, such as hematometra, presence of embryonic remains, excessive bleeding. All these patients underwent vacuum aspiration of the uterine cavity with hemostatic purpose, embryo scrap and blood clots from the uterine cavity were removed. From the anamnesis it was found out that 5 (1%) women had repeated missed miscarriage, repeated induced miscarriage by curettage of the uterine cavity more than once for 26 (7%) patients. Probably the previous damage to the receptor apparatus caused the MA and evolved to chronic endometritis, which led to these complications.

In the comparison group, complications were observed in 12-17% of patients, hematometra in 5 (7.5%) cases, endometritis in 5 (7.5%), embryonic remains in 2 (2%), and this is twice more often than with pharmacological cleaning of the uterine cavity. Women, who had curettage of uterine cavity, got complications such as hematometra and embryonic remains. In this cases, a repeated vacuum aspiration of the uterine cavity was performed.

**Conclusion.** The probable causes of the arisen MA were artificial abortion and spontaneous abortion with subsequent curettage of the uterine cavity, which most likely led to autoimmune chronic endometritis. The most vulnerable period of gestation at the first trimester was the period from 6 to 8 weeks of gestation in 321 (64%) cases, which is probably due to an impairment of the first wave of invasion of the cytotrophoblast into the inferior endometrium with the receptor apparatus damaged. Medical pharmacological termination of MA is one of the safest treatments in the early period at the first trimester with a lower incidence of complications (6%), compared to surgical abortion (17%). Given that the low incidence of complications after the pharmacological cleaning of the uterus during MA in early stages, this method can be proposed to be performed in the outpa-

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