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The articles are given in the authors' translation

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EDITOR-IN-CHIEF COLUMN

Dear Colleagues!

The new 2019 year has begun, which, like all the others, will be eventful, full of the daily creative work of everyone in his place. For the «Yakut Medical Journal» this is the release of four issues, in which the authors not only from the Sakha Republic (Yakutia), but also from other regions of Russia and the near - abroad countries will publish their papers. It should be noted that in 2018 and at the beginning of the year, our journal did not experience a lack of materials that were certainly interesting, relevant and generally quite positively received by users.

We live and work in a very dynamic time. This is a period of further development of the Republic, the country as a whole. There are changes in all spheres of life. There is a search for optimal development paths, where the main criterion is not so much quantitative growth, but a qualitative leap forward.

The Ministry of Education and Science of Russia is constantly working to improve the quality of scientific publications by optimizing the principles of forming the List of peer-reviewed scientific publications, which should publish the main scientific results of dissertations for the degree of candidate and doctor of science (hereinafter referred to as the List). In accordance with the order of the Ministry of Education and Science of Russia dated December 12, 2016 No. 1586, changes were made to the Rules for the formation of the List, Requirements for peer-reviewed scientific publications, approved by order of the Ministry of Education and Science of Russia dated February 12, 2018 No. 99.

The work on the formation of the List is a permanent, continuous process where the scientific specialties, according to which the scientific publication is included in the List, are specified (excluded and/or added). In 2018, the Higher Attestation Commission and the specialized expert councils of the Higher Attestation Commission clarified scientific specialties and branches of science for which scientific publications are included in the List, approved by order of the Ministry of Education and Science of Russia dated December 28, 2018 No. 90-p.

In this regard, there have been some changes in the list of scientific specialties by which the "Yakut Medical Journal" is included in the List.

The editorial board and editorial council of the "Yakut Medical Journal" in 2019 will continue to work on improving the quality of published materials, as well as on compliance with the List of scientific specialties for which "Yakut Medical Journal" is included in the List and which will be announced in the Ministry of Education and Science in the future Russia as a profile.

We will make efforts to improve the site of the journal. The editorial board will be updated.

«Yakut Medical Journal» is and remains to be one of the sought-after by medical community of the Sakha Republic (Yakutia) professional, scientific and practical medical publication. The Journal works with a wide range of regional material, highlights the achievements and problems of practical health care, medical science and medical education in one of the Arctic regions of the Russian Federation. This is its main purpose.

I wish you, our authors and users, good health, well-being and professional achievements!

Let the "Yakut Medical Journal" be an inseparable companion of your professional activity!

Editor-in-Chief Anna Romanova

ORIGINAL RESEARCHES

E.A. Kashuba, M.V. Antonova, T.G. Drozdova, O.A. Ljubimceva, L.V. Hanipova, N.V. Ogoshkova, Ju.S. Chehova

PROGNOSTIC VALUE OF THE DYNAMICS OF THE CYTOKINES IN EPSTEIN-BARR VIRUS INFECTIOUS MONONUCLEOSIS DEPENDING ON THE AGE OF THE CHILD

DOI 10.25789/YMJ.2019.65.02

ABSTRACT

Aim of the study is to reveal prognostic value of dynamics of cytokines in children of different age groups with Epstein-Barr viral infectious mononucleosis.

Material and methods: we conducted a study of 98 children with Epstein-Barr viral infectious mononucleosis, including a comprehensive immunological examination. Statistical data processing was carried out in the «Statistica 10».

Results: in children 3-6 years old was recorded the predominance of Th2 immune response, in children 7-11 years old the type of response was mixed - T1/T2, and in the group of 12-17 years old there was a full launch of Th1 response.

Conclusion: changes in the cytokine profile in the children 3-6 years old can be considered as factors explaining the frequent reactivation of EBV. Complex immunological reaction in the children 12-17 years old can be considered the most favorable response, contributing to the elimination of EBV. The immune response of the children 7-11 years old occupied an intermediate position.

Keywords. Epstein-Barr virus, infectious mononucleosis, children, cytokines, lymphocytes, Th1 immune response, Th2 immune response.

Introduction. The reasons for the active study of Epstein-Barr virus infection (EBVI) are the widespread distribution of the virus, a high percentage of infection in the population, the tropism of EBV to immunocompetent cells, a variety of clinical manifestations, a tendency to chronize the infectious process, the possibility of forming of secondary immunodeficiency or malignant tumors [3, 12, 14]. According to some authors, the factor that determines the failure of the immune response in EBVI is the deficiency of synthesis of proinflammatory cytokines TNF-α, IL-8, IFN-γ against the increased production of IL-4 [6]. Mast cells and basophils produce IL-4, which causes differentiation of CD4+Th-0 in Th-2 [4, 8]. IL-4 and IL-10 play an important role in shifting the immune response towards humoral response. It depresses the production of IFN-γ and the activity of IL-2 and leads to inhibition of cell-mediated immune response [2, 13]. Such cytokine shifts cause a restriction of the intensity and prevalence of the inflammatory process in various organs, but violate the processes of sanogenesis. It leads to the development of recurrent, chronic forms of EBVI, WEB-associated lymphoproliferative diseases and autoimmune pathology [1, 7, 10]. Opposite, the favorable course of EBVI is accompanied by an increase the level of α-IFN, γ-IFN, IL-1β and TNF-α, and consequently a shift in the immune response towards Th1 [5, 9, 11]. Thus, it was found that the relation of cytokines in the blood of a child with EBV is an informative criterion for the severity of the course and prognosis of the outcome of the disease. However, comprehensive information concerning the age features of immunological shifts as criteria of prognosis absents in the literature.

Aim of the study is to reveal prognostic value of dynamics of cytokines in children of different age groups with Epstein-Barr viral infectious mononucleosis.

Materials and methods of research. A dynamic prospective cohort study of 98 children with laboratory-confirmed diagnosis of infectious mononucleosis due to primary Epstein-Barr viral infections was conducted. We formed 3 age groups: I group - 3-6 years (n=29), II group - 7-11 years (n=25) and III group - 12-18 years old (n-45). The criteria for exclusion from the study were the absence of markers of active EBV infection: detection of markers of the activity of other herpes viruses; the presence of symptoms of exacerbation of comorbidity; refusal of legal representatives to participate in the study. The control group included 20 immunologically healthy children. Immunological examination of patients was carried out at the 1st and 3rd week of the disease and consisted of determining the concentration of cytokines (IL-1, IL-2, IL-4, IL-6, IL-10, IFNɣ, TNFa). We performed statistical data processing using the application package “Microsoft Office” and “Statistica10”. According to the results of the Shapiro-Wilk criterion, we found that the distribution of some indicators was different from normal. As a result of it, we expressed the values of indicators like the median, 25th and 75th percentiles (Me (C25-C75)). We tested the hypothesis about the equality of two Me using the Wilcoxon test (for dependent samples) and the Man-Whitney test (for independent samples). The critical level of statistical significance (p) was 0.05.

Results and Discussion. Assessment of age-related peculiarities of cytokine profile at the 1st week of the disease revealed that the content of IL-1, the main proinflammatory cytokine, decreased in children 3-6 years and increased in older age groups (PII=0,034). According to some authors, the absence of pronounced stimulation of synthesis IL-1 in patients with IM can be associated with the inhibitory effect of IL-1RA. The EBV induces the production of IL-1RA in neutrophils. It leads to the insufficiency of IL-1 dependent mechanisms of cellular immunity [8]. A similar trend was evidence of delayed reaction of the immune system of children of preschool age on the replication of EBV (Table 1).

The level of the IFN-γ, inducer of the cellular immune response, was higher in all children in the initial period of the disease than the control group. This increase was statistically significant in children aged 3-6 and 7-11 years (pI=0.000; pII=0.02). The level of IL-2, which plays a role in the early proliferation and differentiation of lymphocytes, significantly decreased in children 3-6 years and increased in children 12-17 years (pI=0,000; pIII=0,004). A similar trend was observed for TNF-α, another mediator synthesized by CD4+ LF type 1 (Th-1) (pI=0.000; pIII=0.000; pI-III=0.03)

(table 1).

Consequently, in children under 12 years on the 1st week of IM developed a deficiency of Th1 immune response. It consisted of a significant reduction of Th1 cytokines (IL-2, TNF-a) and increase in the production of cytokine, triggering the processes of differentiation of Th0 B-lymphocytes in Th1 (IFN-ɣ). A full start of Th1 immune response, manifested by an increase in the level of all Th1 cytokines, occurred in children over 12 years (Table 1).

On the state of the Th2 immune response we tried according to the contents of its major cytokines. The level of IL-4 increased in children under 11 years (pI=0.000; pII-III=0.026). IL-6 increased many times in children of all age groups. Maximum level of IL-6 recorded in children older than 12 years (pI=0,000; pII=0,000, pIII=0,007). The content of another important mediator of Th-2 immune response (IL-10) was significantly high in comparison with the control group (pI=0.000; pII=0.000; pIII=0.000) and inversely proportional to the child's age (PI-III=0.042) (table1).

Thus, the maximum level of Th2 cytokines at the 1st week of IM was observed in children 3-6 years. Such shift in the immune response is a risk factor for difficulty eliminating EBV in the acute period of the IM (Table 1).

In the retest of cytokine profile in children 3-6 years was significantly higher content of IL-1 (pI-II=0,020), compared with older age groups. This indicated the absence of subsiding immune inflammation in the body of young children (Table 2).

The level of production of IFN-ɣ, an inducer of Th-1 immune response, was inversely to the age of children (pI=0.037). The content of IL-2 in all groups was significantly smaller compared to the control index (pI=0.000, pII=0.000, pIII=0.000). However, in the dynamics of the disease production of the cytokine increased in children under 12 years old and was significantly reduced in adolescents. The content of TNF-ɣ in different groups changed similarly (pII=0.002; pIII=0.015; pI-III=0.004) (Table 2).

Consequently, at the 3rd week of IM in children 12-17 years old there was a decrease in the activity of mediators of Th1 immune response. Children of 3-6 years old showed features of disbalance in cell-mediated immune response.

The content of IL-4, the key cytokine of Th2 immune response, remained repeatedly elevated in children of all age groups (pI=0,016, pII=0,000). The level of IL-6 decreased in dynamics. At the same time, in children of 7-11 years old this change was statistically significant in comparison with the control group (pI=0.016, pII=0.000). Production of IL-10 decreased inversely to the age of the child. However, the level of this cytokine at the 3rd week of IM was still significantly high (pI=0.000, pII=0.000; pIII=0.008) (Table 2).

As a result, the level and ratio of cytokines on the 3rd week of IM testified to the dominance of Th2 immune response in all groups. At the same time, the continued elevated level of IL-1 in children 3-6 years old indicated the absence of subsiding immune inflammation.

Based on the data obtained, we can conclude that the optimal response of the immune system to EBV infection develops in older children. It provides activation in the early stages of Th1, fast switching to Th2, its dominance at a later term and a gradual subsiding. Insufficiency of the cellular component, excessive activation of the humoral and increased the level of proinflammatory cytokine IL1 during remitting clinical symptoms were detected in children of preschool age. These factors may cause frequent re-activation of EBV in this age group. The type of immune response in children 7-11 years old had an intermediate character.

Conclusion. In children 3-6 years old were revealed a long-term persisting production of proinflammatory cytokines, predominance of Th2 immune response in the early stages of the IM and its excessive activation in the subsiding symptoms period. These changes can be seen as factors that explain the frequent reactivation of EBV in preschool children.

In the group of 12-17 years old the dynamics of cytokine profile consisted of the activation of Th1 immune response, followed by switching to Th2. This response, in our opinion, is the most favorable response of the macroorganism, contributing to the elimination of EBV.

In children 7-11 years old cytokine profile in the initial period of IM characterized by an active production of Th1 and Th2 cytokines and earlier switching to the humoral response. Apparently, such reaction of the immune system is sufficient to deter the active replication of EBV in the period of long-term convalescence.

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Table 1

Cytokine profile of children at the 1st week of EBV IM

Cytokine	Группа							
	control group		I group 3-6 years old		II group 7-11 years old		III group 12-17 years old	
	Me	25% 75%	Me	25% 75%	Me	25% 75%	Me	25% 75%
IL-1	0,29	0,10 0,53	0,0	0,0 0,90	0,87**	0,15 1,59	0,74	0,38 1,72
IFNɣ	6,70	4,20 14,80	10,90***	10,90 20,50	16,60*	3,60 19,80	11,90	0,0 23,80
IL-2	11,85	8,65 15,0	0,0***	0,0 0,0	0,0	0,0 0,0	57,26**	1,50 60,80
TNFα	17,61	3,65 13,53	1,70***	1,10 5,60	*0,40*	0,30 0,90	*61,70***	47,30 72,89
IL-4	0,008	0,0 0,01	0,20***	0,10 0,20	*0,12*	0,02 0,30	*0,0*	0,0 0,20
IL-6	0,004	0,001 0,005	4,60***	4,60 5,30	8,60***	3,85 9,93	14,89**	5,80 18,90
IL-10	1,65	1,23 1,84	31,30***	31,30 36,70	12,41***	10,2 26,96	13,20***	10,44 18,30

Note: * - statistically significant differences with the control group (p≤0.05; p≤0.01; p≤0.001); 1.70 –between I and III groups (p≤0.05); 0.40 - between II and III groups (p≤0.05).

Table 2

Table 2 Cytokine profile of children at the 3rd week of EBV IM

Cytokine	Группа							
	control group		I group 3-6 years old		II group 7-11 years old		III group 12-17 years old	
	Me	25% 75%	Me	25% 75%	Me	25% 75%	Me	25% 75%
IL-1	0,29	0,10 0,53	1,20	0,25 2,05	0,0	0,0 0,0	0,0	0,0 1,20
IFNɣ	6,70	4,20 14,80	16,35**	6,40 32,0	10,60	0,0 16,60	5,90	0,0 18,70
IL-2	11,85	8,65 15,0	0,30***	0,0 1,25	1,0***	0,0 2,10	0,0***	0,0 0,30
TNFα	17,61	3,65 13,53	3,65	1,70 49,35	0,20**	0,0 21,50	0,30*	0,0 2,50
IL-4	0,008	0,0 0,01	0,25*	0,0 0,55	0,30***	0,20 0,70	0,14	0,0 0,10
IL-6	0,004	0,001 0,005	4,50**	0,0 18,45	0,0*	0,0 0,30	5,6	0,0 9,0
IL-10	1,65	1,23 1,84	24,30***	15,50 26,65	8,30***	5,0 11,70	5,60	4,73 12,30

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T.V.Polivanova, V.A.Vshivkov

ASSOCIATION OF THE INDICES OF CIRCULATING LEPTIN WITH GASTRITIS CLINICAL MORPHOLOGICAL SIGNS DEPENDING ON BODY MASS INDEX IN SCHOOLCHILDREN WITHOUT OBESITY

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ABSTRACT

Aim: to study the association of leptin circulating in blood with gastritis clinical morphological signs in schoolchildren with normal and excessive body mass index.

Materials and methods: we have examined 46 schoolchildren with gastric intestinal complaints, patients of Gastroenterologic Division with preliminary diagnosed gastritis, followed by morphological tests, which confirmed the diagnosis in all the children. There were two cohorts of the subjects: with normal body mass (1st cohort, n = 31), with excessive body mass (2nd cohort, n = 15). All the subjects have passed: gastroscopy, including biopsy sampling, identification of the level of leptin circulating in blood serum by immune enzyme method fasting.

Results: The analysis of the results of the tests showed the increase of leptin level in schoolchildren in the 1st cohort with the clinical signs of dyspepsia (2.2 (0.1 – 8.4) ng/ml as compared to 0.1 (0.1 – 0.1) ng/ml in children without dyspeptic complaints; p = 0.443), that proves the strengthening of the hormone regulating role. At the same time the dynamics of leptin indices and their association with destructive changes in gastric mucosa, gastritis activity and *Helicobacter pylori* infection hadn't been marked. In the 2nd cohort no associations with gastritis clinical morphologic signs had been revealed. Besides, in the schoolchildren of the 2nd cohort we didn't find any increase of the level of circulating leptin in the presence of dyspepsia clinical sympathocomplex. That is why in the 2nd cohort the level of leptin in blood serum was considerably higher, than in the 1st cohort.

Conclusion: In children with excessive body mass the gastritis and associated pathologic processes in gastric mucosa are being formed and developed under the conditions of hyperleptinemia, because the level of its secretion into blood substantially depends on the volume of fat tissue in an organism. Leptin involvement and the strengthening of its regulating role, which is determined in children with normal body mass with dyspeptic symptoms are balanced under the conditions of the increase of fat tissue quantity in an organism.

Keywords: leptin, dyspepsia, gastritis, children, *Helicobacter pylori*, body mass index.

During the last years the list of the factors which considerably influence the course of gastroduodenal diseases involve obesity [15, 18]. In different regions of Russian Federation from 45 to 62 % of adult population suffer from obesity or overweight. The prevalence of obesity and overweight in Russia is rather high, but this index is different in different populations [5]. Among children the index is lower and it is 5.6 % (obesity) and 19.9 % (overweight) on average with considerable variations in accordance with gender and age [9]. Traditional understanding of the functions of fat tissue in an organism had changed. Active role of adipocytes of fat tissue in the synthesis of many peptides had been determined, including those with hormone activity. One of them is leptin [7, 17], a hormone, which has wide functional application in an organism [20]. Up to the present moment it has been shown that in addition to the control over nutrition behavior this hormone (leptin) influences the state of central nerve system, it also influences pancreatic gland, kidneys, immune and sympathetic nerve system. High level of leptin in plasma is accompanied by the activation of sympathetic nerve system, endothelial dysfunction, oxidative stress and so on [20]. The level of the indices of leptin which circulates in blood is associated with the volume of fat tissue in an organism [6]. During the last years scientists have marked negative influence of obesity on the development of diseases, including those of digestive tract [18] with hyperleptinemia as pathogenetic link. Now its role in the gastric cancer development is being actively studied [15, 18]. At the same time many aspects of hyperleptinemia association with digestive tract diseases are not studied well-enough.

Considering regulatory role of leptin, including pathology processes, definite interest is paid to the issues related to the association of circulating hormone with dyspepsia, pathophysiologic mechanisms of many aspects of its formation are still not clear [3, 8]. The data in regard to the ratio blood leptin indices/ gastritis clinical morphological signs in children, especially on the initial stage of gastritis formation in association with body mass. These became the basis for carrying out the present research.

Aim: search for the association of circulating leptin with gastritis clinical morphologic signs in schoolchildren with normal and excessive body mass index.

Materials and Methods. We carried out clinical examination for 46 schoolchildren, all of them being the patients of Gastroenterology Division including interviewing in regard to dyspeptic complaints. Tests had been carried out in the Clinical Division of «Scientific Research Institute for Medical Problems of the North» with the permission of ethics authorities. All the patients who took part in the research had signed the informed concern form related to the experiment in accordance with World Medical Association's Declaration of Helsinki, regularizing scientific research.

All the children have been performed gastroscopy with biopsy sampling from the antrum of the stomach for morphological tests of the mucosa. Gastritis as diagnosis was confirmed by the said tests.

Criteria for the subjects to take part in the research: 1. Gastritis in different forms diagnosed by endoscopic test (erythematosus, nodular, gastritis with erosions), morphologically confirmed; 2. Ages from 7 to 17 years; 3. Absence of acute inflammatory diseases within the last month; 4. Absence of chronic diseases in other systems of an organism in the acute stage; 5. Absence of functional insufficiency in other organs and systems; 6. Conformity with normal body mass index (BMI) and/or excessive body mass.

Criteria for rejecting from the research: 1. Age younger than 7 years or elder than 17 years; 2. Acute diseases of inflammatory genesis within the previous month; 3. Chronic diseases in other systems of an organism in an acute stage; 4. Functional insufficiency in other organs and systems of an organism. 5. BMI is lower than under norm or in obesity.

Taking into account body mass index we have analyzed two cohorts of children: 1st – with normal BMI indices;

2nd – with BMI corresponding to excessive body mass. BMI calculation was carried out using BMI formula = Weight (kg) / Height $(m)^2$ [11]. Gender and age in schoolchildren were the same between cohorts. Evaluation of body mass indices was performed according to corresponding indices, shown in WHO percentile tables and BMI standard deviations. We took into account height, body mass, gender and age of a child. Considering WHO recommendations and in accordance with federal clinical recommendations, obesity in children and adolescents in the ages from 5 to 19 years was identified as BMI equal or over +2.0 SDS BMI, and excessive body mass as BMI from +1.0 to +2.0 SDS BMI [1, 4, 16].

The majority of the examined children with gastritis (82.6 %) showed dyspepsia clinical signs. The presence of dyspepsia syndrome (non-examined dyspepsia) was evaluated when there were complaints related to pain or discomfort feeling in epigastrium, nearer to median line. When estimating clinical course of dyspepsia we used the variants offered by Rome criteria. We recognized two variants of the course of the disease: 1) syndrome of epigastric pain – when schoolchildren had pains or burning sensations in epigastrium, without permanent character, which was found in 52.6 % of dyspepsia children; 2) postprandial distress syndrome – when after meals with accustomed quantity of food children fell postprandial fullness in epigastrium or early saturation, which were found in 47.4 % of the children with dyspeptic complaints [13]. The present research didn't touch gastrointestinal tract functional disorders according to Rome criteria, because all the children had verified gastritis.

Morphologic tests for bioptats of gastric mucosa involved light microscopy after gematoxyllin-eosin coloring. Gastritis diagnostics was carried out in association with the presence of neutrophil infiltration of epithelium and/or own plates in accordance with Sydney classification, which involves determination of 3 stages in the activity of inflammatory process. The 1st stage matches to moderate leucocyte infiltration of own plates of mucosa. The 2nd stage matches to more expressed infiltration and it covers epithelium in addition to own plates. The 3rd stage matches to expressed infiltration and in addition «abscesses» [2]. According to Modified Sydney Classification we estimated the presence of atrophic gastritis [12]. We haven't found any cases among the examined subjects. *H. pylori* presence was determined after the Gimza coloring of biopsy sections of antral mucosa [2].

In all the children, involved into the research, we identified the concentration of leptin in blood serum. Blood sampling for determining the concentration of circulating leptin was performed from 8 to 10 hours a.m. after night fasting. Leptin content in blood serum was calculated by immune enzyme method with the help of manual pad using the set of chemical agents Human Adiponectin ELISA, producer BioVendor. Leptin indices in the samples have been defined according to the producer's instructions. Leptin indices in children and adolescents didn't exceed the reference meanings separately for boys and girls in four age groups (6-9 years, 9-12 years, 12-15 years, 15-20 years).

Statistical analysis of the results was carried out with the help of program pack Statistica 6.1 (StatSoft, the USA). Checking for the distribution of the indices with the help of Shapiro – Wilks test showed their distinctions as compared to the norm, which caused the implementation of non-parametric methods of statistics. Cohorts were compared with the help of Mann-Whitney criterion. Statistical meaningfulness of the differences between the signs was evaluated under $p<0.05$ [10].

Results and discussions. Our findings show that the indices of leprin circulating in blood were considerably higher in children with excessive body mass (25.8 (13.9 – 43.5) ng/ml) as compared to the children with normal body mass (0.1 (0.1 – 6.5) ng/ml; p= 0.0001). This is quite explainable because at present it is well-known that leptin producers are adipocytes and the level of hormone, which secrets into an organism is directly associated with fat tissue mass. It is very important to mark that as a whole children with excessive body mass show wider fluctuations of leptin indices (from 0.1 to 52.6 (ng/ml)). There is scientific data specifying that as a rule obese subjects demonstrate insulin-resistance, which allows supposing that the increase and expressed range of the indices of leptin circulating in blood serum in children with excessive body mass can serve as the first sign of the formation of leptin-resistance in a range of them, which is associated with the lowering of slowing down influence of the hormone on appetite with the participation of central mechanisms.

From one side leptin is considered to play regulatory role in regard to physiological processes in an organism by influencing vegetative nerve system. From another side, numerous data had been accumulated related to its pathogenetic role in the formation of gastrointestinal tract diseases. In this connection we have analyzed the results in terms of the association between the level of the hormone circulating in blood and dyspeptic signs, that is with pathologic process. In its formation as it is known, the dysfunction of regulatory mechanisms plays not the last role with nerve system involved. At the same time we haven't found any association between leptin indices and dyspeptic syndrome, both with its presence and clinical course. But, we had some findings after analyzing the issue taking into account weight-height leptinh indices. In particular, in children with normal BMI dyspeptic complaints were associated with the increase of leptin circulating in blood (Table 1). This result proves leptin influence on the pathology in the way of its participation in the neuro-hormone regulation. At the same time in overweight children we didn't mark any association between leptin indices with dyspeptic syndrome. In them the indices of circulating leptin are considerably higher, despite the presence of dyspepsia symptomocomplex and its clinical course. That is why we didn't find any increase of the meaningfulness of leptin hormone regulation in an organism in excessive body mass children with dyspeptic syndrome, which is probably explained by its excessive production by fat tissue. So, leptin participation in the regulation of pathology process, which is the basis of dyspeptic syndrome in children, is associated with body mass. This can cause peculiarities in the risks of the formation and clinical course of pathology process in the subjects with different body mass. Taking into account leptin metabolic effect in the subjects with excessive fat tissue, its influence can be distributed to morphologic-functional state of a stomach, including its mucosa, but in the long-time course, with the formation of metabolic disorders.

Taking into account new data on the association between circulating leptin indices and carcinogenesis processes, it becomes very important to pay attention to the association between its level and gastric activity, *H. pylori* infection, which are considered to be ethiopathogenic links in the formation, atrophy and metaplasia of gastric mucosa, each with the meaningful influence upon the named processes. We believe those data is of interest in terms of the age, including childhood and adolescence period in the life of individuals.

Association of blood leptin with gastritis (gastritis forms and macro morpho-

Table 1

Leptin level in blood in children due to the presence of dyspeptic complaints

Children		Leptin level						p1-2
		Normal BM		Excessive body mass		Total		
		n	Me (C25-C75)	n	Me (C25-C75)	n	Me (C25-C75)	
1. Without dyspepsia syndrome		7	0,1 (0,1-0,1)	1	52,6 (52,6-52,6)	8	0,1 (0,1-1,5)	
2. With dyspepsia syndrome		24	2,2 (0,1-8,4)	14	22,9 (13,9-35,2)	38	6,3 (0,1-20,1)	0,0003
Clinical course	Epigastric pain syndrome	14	0,5 (0,1-6,5)	6	28,5 (3,3-33,5)	20	3,0 (0,1-18,0)	0,0087
	Postprandial distress-syndrome	10	3,3 (0,1-15,2)	8	18,8 (14,7-39,9)	18	14,6 (2,2-20,1)	0,0266
P1-2	0,0443		0,0466					
P3-4	0,2847	0,9497	0,206					

logic changes in endoscopic tests) hasn't been revealed (Table 2).

The most actual moment in the analysis of the results of our study was the evaluation of the association between the level of leptin circulating in blood with the activity of inflammatory process in stomach mucosa, because it is high activity, which to a large degree causes unfavorable gastritis course. When analyzing the obtained data we haven't found any association between the two parameters (Table. 3). At the same time gastritis, which is the start of carcinogenesis, in children with deviations in height-weight indices in the stage of excessive body mass is developing under the conditions of the expressed liptinemia, which can contribute to the formation of atrophic changes in stomach mucosa. But critical level of hyperleptinemia and its duration, when cancer morphologic changes can be expected in stomach mucosa.

There is scientific data specifying that obesity increases the risk of stomach cancer diseases development, first of all it concerns atrophic gastritis, but the mechanisms of this association are still unclear to great extent. Nevertheless leptin involvement is demonstrated in the range of scientific works. So, some research with the implementation of experimental models had demonstrated that lipotoxicity is the factor of pre-cancer disorders, accompanied by the disturbance of organelle homeostasis, tissue integrity and the change in gene expression of stemness of stomach epithelium. As a result it was characterized by atrophic changes in gastric mucosa [15, 18].

It is likely that in addition to immune response in the time of the development of progressive inflammatory process, there can also exist metabolic aspects in the formation of atrophy in the stomach mucosa, by which leptin realizes its effect towards carcinogenesis risks, in the first turn under the conditions of hyperleptinemia. Unquestionably those points of view require proof and further studies.

In the course of the study we also didn't mark any association of the level of circulating leptin with *Helicobacter pylori (H. pylori)* infection in children both with normal and excessive body mass (Table 4). Pathogenic role of *H. pylori* bacteria in the formation of atrophic processes is a proven fact. Besides it is categorized as a factor, activating carcinogenesis process [14]. In this connection both infection and leptin are regarded as active participants of pathophysiological process of gastric carcinogenesis. However various research aimed at studying leptin involvement into the course and progress of infection-associated gastritis in adults show controversial results [19].

Undoubtedly all the above listed to greater extent concerns the issues of carcinogenesis in subjects with obesity. At the same time leptin production in gastritis in patients without obesity has not been studied enough. The data on the hormone influence on the gastritis course, especially on its progressing, would assist in the understanding of its pathophysiological role in carcinogenesis. In children this issue has not been studied as well. But to our minds, it is particularly relevant as pathology process is not from its source. While analyzing the results of our research aimed at the association of leptin level with gastritis clinical morphologic signs we marked that in children leptin influence on gastritis clinical morphological signs to great extent concerns regular processes. In this respect the evaluation of leptin involvement in hormone regulation of this or that pathological or physiological process in organism is difficult, because the level of its secretion into blood considerably depends from the volume of fat tissue in an organism [6, 7]. Certainly the issue requires further consideration.

Conclusion. Gastritis children with dyspeptic complains show increased level of leptin in blood plasma, which can be explained by its regulating influence on vegetative nerve system and this relates to normal BMI only. Whereas the association of leptin indices with gastritis morphologic forms, its activity and *H. pylori* infection has not been found. In this context gastritis, which is the starting point of carcinogenesis in children with deviations related to height-weight parameters in the stage of excessive body mass is developing under the conditions of hyperleptinemia. Nevertheless there is no data available on hyperleptinemia level and duration, which could be regarded as critical for expecting pre-cancer morphological changes in gastric mucosa. Clear-

Table 2

Association of blood leptin indices with gastritis endoscopic forms

Children	Gastritis with erosions		Non-erosive gastritis forms (erythematosus + nodular)		p1-2
	n	Me (C25-C75)	n	Me (C25-C75)	
1. With excessive body mass	3	25,8 (15,4-49,1)	12	25,7 (8,6-39,4)	0,7341
2. With normal body mass	7	0,9 (0,1-3,5)	24	0,1 (0,1-6,6)	0,9448
3. Total	10	2,9 (0,1-15,4)	36	3,2 (0,1-18,8)	0,9895
p1-2	0,0167		0,0004		

Table 3

Association of blood leptin indices with the activities of antral gastritis in children

Children	Activity at 1st stage	Activity at 2nd – 3rd stages	p1-2		
	n	Me (C25-C75)	n	Me (C25-C75)	
1. With excessive body mass	6	38,5 (17,4-49,1)	9	22,9 (9,4-33,2)	0,2284
2. With normal body mass	10	0,5 (0,1-6,5)	21	2,2 (0,1-6,6)	0,7992
3. Total	16	10,2 (0,1-31,9)	30	3,1 (0,1-15,4)	0,4266
p1-2	0,0008	0,0008			

Table 4

Association of leptin indices in blood in *H. pylori* children

Children	*H. pylori* +	*H. pylori* -	p1-2		
	n	Me (C25-C75)	n	Me (C25-C75)	
With excessive BM	8	17,8 (8,6-30,5)	7	33,5 (17,4-49,1)	0,2319
with normal BM	18	0,1 (0,1-3,1)	13	0,9 (0,1-10,2)	0,4175
Total	26	2,8 (0,1-13,9)	20	8,4 (0,1-30,7)	0,2957
p1-2	0,0006	0,0007			

ly, carrying out further research aimed at meaningful mechanisms of hyperleptinemia influence on carcinogenesis in stomach mucosa is topical.

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A COMPARATIVE ANALYSIS OF THE EXPERIMENTAL INDICATORS OF INTRACUTANEOUS OXYGEN TENSION WITH MICROCIRCULATION PARAMETERS

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ABSTRACT

The article presents the results of the authors' research on the modern possibilities of studying a number of hemodynamic parameters – microcirculation and oxygen tension (PO2) in the skin of the abdomen in rats.

To conduct qualitative and quantitative analysis of microcirculation in experiments on animals using laser Doppler flowmetry and transcutaneous oxygemometer experiments have been performed in 25 mature male rats of Wistar line. The control group consisted of 5 rats. Animals of the experimental group were tired daily for 30 days by forced running from 0.5 to 1.0 hour at a speed of 10-15 km/h. A time of the rats' running on the treadmill depended on the intensity and productivity of their run. On the first day and in 5, 10, 20 and 30 days from the beginning of the experiment microcirculation speed was studied in the skin of the abdomen of the animals after the running load with «Transonic Systems Inc.»(Model BLF21) laser Doppler flowmeter as well as intradermal oxygen tension with Radiometer TCM-2 (Denmark) transcutaneous oxygemometer. It was found that during the experiment in animals of the experimental group the level of intracutaneous oxygen tension was lower than in control animals. It was found that in systematic running load the microcirculation in the skin of the animal's abdomen accelerated up to 10 days from the beginning of the experiment. Then, by 30th day there was a slowdown in the rate of microcirculation. But in all measurements during the experiment it was faster than in animals of the control group. The inverse dependence of PO2 from the rate of microcirculation was revealed, which was expressed by a decrease in the level of intracutaneous PO2 in all cases of increasing the rate of intracutaneous microcirculation.

The study has showed that the study of hemodynamic parameters of experimental animals with the research methods described above is a promising direction of modern physiology. The main advantages of these research methods are noninvasiveness, which provides the possibility of repeated use in the experiment and the implementation of dynamic control over changes in the studied parameters.

Keywords: microcirculation, oxygen tension, experimental study.

Introduction. Interest in the study of hemodynamics in animal experiments involves extrapolating the results to humans. The experimenter has an extensive arsenal of devices that record various parameters of tissue and organ hemodynamics. A particular interest are the devices that make it possible to perform noninvasive methods of hemodynamic studies in organs and systems of laboratory animals in the process of experimental exposure [1, 3, 4, 7, 8]. The simplest, most accessible, and noninvasive hemodynamic studies in animals are performed using Doppler ultrasound scanning [2, 5, 6, 9-11]. In addition, various analyzing systems based on laser Doppler flowmetry are used to study blood microcirculation in laboratory animals, and transcutaneous oxygemometers and polygraphs are used to determine intracutaneous oxygen tension [7, 8]. The choice of a device for the study of hemodynamics in a particular vascular pool depends on the goal of the study and the devices available to the experimentalist recording hemodynamics [5]. This raises the question of the aim of a particular device's use in a particular experimental study. In the literature, these issues are presented insufficiently, so it involves special studies aimed at conducting a comparative analysis of the results obtained with the use of different recording systems.

The aim of the study was to carry out a comparative analysis of intracutaneous oxygen tension indicators with parameters of microcirculation in the skin of the abdomen of the experimental animals.

Materials and methods of research. The study was performed in 20 mature male Wistar rats weighing 280-300 g or more. The control group consisted of 10 rats. Animals of the experimental group were tired daily for 30 days by forced running from 0.5 to 1.0 hour at a speed of 10-15 km/h. A time of the rats' running on the treadmill depended on the intensity and productivity of their run. On the first day and in 5, 10, 20 and 30 days from the beginning of the experiment oxygen tension (PO2) was measured in the animals' skin of the abdomen in the control and experimental groups under general anaesthesia (1% solution of thiopental sodium at the rate of 15 mg/kg of body weight intraperitoneal) in the supine position by means of transcutaneous oxygemometer Radiometer TCM-2 (Denmark) [7], and using «Transonic Systems Inc.»(model BLF21) lazer Doppler flowmeter (LDF) device. Parameters of intracutaneous microcirculation were determined [8].

To determine the PO2 wool in the rat's abdomen was shaved, the skin was treated with soap and water, dried with ether and degreased. The sensor retainer was glued to the skin the cavity of which was filled with a contact gel and sealed with a membrane. Calibration of the device sensor was performed, which was stopped after the appearance of a stable indicator on the display of the device. After the device calibration finishing, the sensor was fixed in the lock and a series of measurements were performed (Fig. 1).

When determining the parameters of intracutaneous microcirculation with the help of LDF, recording of indicators began after a 10-minute adaptation of the animal to an ambient temperature of 20°C. Indications of intracutaneous microcirculation were measured for 5 minutes in the area of the shaved part of the anterior abdominal wall (the site of determining the skin PO2) until a stable value was achieved.

Care of animals was carried out according to the orders regulating the organization of work with use of experimental animals.

Digital data were processed by meth-

ods of variation statistics using Microsoft Excel licensed computer program.

Results and discussion. The initial level of PO2 in the abdominal skin of the control animals ranged from 27-39 mm Hg (34.2±4.76 mm Hg). On the 5th day from the beginning of the experiment, PO2 level was 28-42 mm Hg (35.6±5.08 mm Hg), in 10 days - 29-44 mm Hg (36.9±6.02), in 20 days - 27-40 (35.2±4.95) in 30 days - 28-41 mm Hg (35.1±5.66 mm Hg). The average value of PO2 in the abdominal skin of the control animals was 35.66±1.00 mm Hg (Fig. 2).

In animals of the control group, the rate of microcirculation in the skin of the abdomen on the 1st day of the study ranged from 13 to 18 ml/100 g/min (15.4±2.07 ml/100 g/min), on the 5th day of the study, the index ranged from 13 to 21 ml/100 g/min (16.3±3.13 ml/100 g/min), on the 10th day – from 13 to 22 (16.8±3.42), on the 20th day - from 13 to 19 (15.8±2.39), on the 30th day - from 14 to 20 ml/100 g/min (16.2±2.28 ml/100 g/min). The average rate of microcirculation in the skin of the abdomen was 16.02±0.58 mm Hg (Fig. 3).

A comparative analysis of the results obtained in the animals of the control group revealed a direct correlation between the parameters of PO2 and the parameters of intradermal microcirculation. The correlation coefficient and its error (R±r) indicated a direct strong and reliable relationship between the change in PO2 and the change in intradermal microcirculation (R±r=0.926±0.071 at p<0.001).

In animals of the experimental group prior to the experiment, PO2 level in the skin of the abdomen ranged from 27-41 mm Hg (34.2±4.76 mm Hg at p<0.01). After running load PO2 was in the range of 26-38 mm Hg (33.4±5.18 mm Hg at p<0.05), which was 1.026±0.028 times lower than the baseline (R±r=0.989±0.011 at p<0.001).

After a 5-day experiment, PO2 level decreased by 1.072±0.126 times (R±r=0.859±0.131 at p<0.001) and was 26-39 mm Hg (33.6±5.18 mm Hg at p<0.05). After 10 days from the beginning of the experiment, PO2 sharply decreased to 22-34 mm Hg (27.6±4.93 mm Hg at p<0.05), that is 1.300±0.129 times lower than the initial level (R±r=0.821±0.163 at p<0.05). On the 20th day of PO2 rose sharply to 24 to 37 mm Hg (31.2±5.63 mm Hg at p<0.05), that is 1.149±0.096 times lower than the initial level (R±r=0.895±0.099 at p<0.01). In 30 days from the start of the experiment, the PO2 was in the range of 26 to 37 mm Hg (33.2±4.71 mm Hg at p<0.01), that is 1.072±0.036 times lower than the initial level (R±r=0.976±0.024 at p<0.001).

The level of PO2 in the abdomen's skin of animals of the experimental group varied during the experiment from 22 to 39 mm Hg (31.8±5.40 mm Hg at p<0.05). On the 10th day it reduced to 27.6±4.93 mm Hg, and by the 30th day it increased up to 33.2±4.71 mm Hg, but in all cases it was below the initial level (Fig. 3).

In animals of the experimental group on the first day of the experiment after a running load, the microcirculation index in the skin of the abdomen ranged from 11 to 23 ml / 100 g/min (18.8±4.76 ml/100 g / min at p<0.05), which was 1.207±0.203 times higher than the control value (R±r=0.896±0.099 at p<0.01). On the 5th day of the experiment, the rate of microcirculation in the skin of the abdomen ranged from 14 to 23 ml / 100 g/min (18.2±4.55 ml/100 g / min at p<0.05), that was 1.103±0,123 times higher than the control value (R±r=0.906±0.091 at p<0.01). On the 10th day of the experiment, the rate of microcirculation in the skin of the abdomen ranged from 14 to 22 ml / 100 g/min (19.2±3.35 ml/100 g / min at p<0.01), which was 1.151±0.130 times more than the control (R±r=0.812±0.170 at p<0.01). On the 20th day of the experiment, the rate of microcirculation in the skin of the abdomen ranged from 13 to 21 ml/100 g/min (18.2±3.35 ml/100 g/min at p<0.05), which was 1.148±0.097 times higher than the control value (R±r=0.914±0.083 at p<0.001). On the 30th day of the experiment, the rate of microcirculation in the skin of the abdomen ranged from 12 to 21 ml / 100 g/min (17.2±3.42 ml/100 g / min at p<0.05), that was 1.057±0.124 times higher than the control value (R±r=0.859±0.131 at p<0.05).

Microcirculation in the skin of the abdomen of animals of the experimental group changed during the experiment from 11 to 23 ml / 100 g / min (18.3±3.89 ml / 100 g/min) on the 10th day it increased to 19.2±3.35 ml/100 g/min, and by 30 days it decreased to 17.2±3.42 ml/100 g / min, but in all cases it was faster than the initial level (Fig. 3).

The comparative analysis of the results obtained in animals of the experimental group revealed the inverse correlation of PO2 parameters with the parameters of intradermal microcirculation. The correlation coefficient and its error indicated at the inverse strong and reliable relationship between the change in PO2 and the change in intradermal microcirculation (R±r=-0.904±0.177 at p<0.05).

Conclusion. The study showed that the microcirculation and oxygen tension (PO2) study in the skin of experimental animals presupposes widespread use of

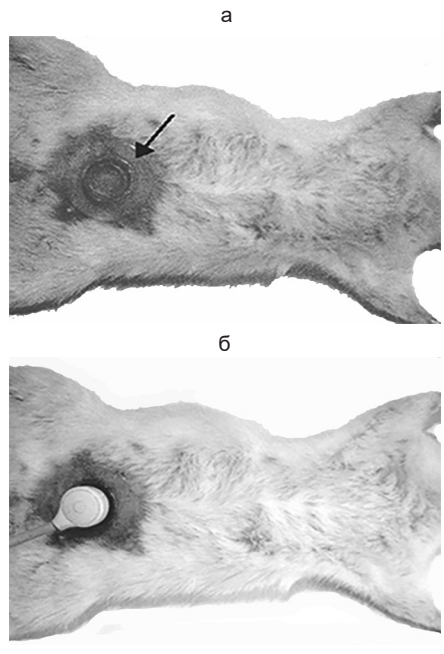

Fig. 1. Measurement of PO2 by transcutaneous method: a – preparation of animals for the measurement of PO2, sensor lock is shown by arrow; b – measurement of PO2 (the sensor is fastened in the locking mechanism).

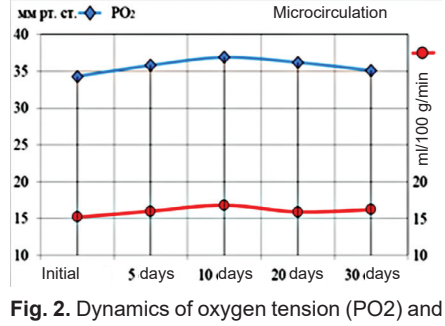

Fig. 2. Dynamics of oxygen tension (PO2) and microcirculation in the skin of the abdomen of the animals of the control group

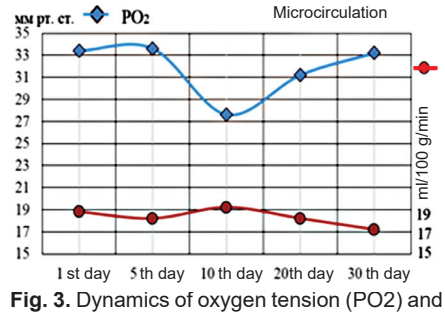

Fig. 3. Dynamics of oxygen tension (PO2) and microcirculation in the skin of the abdomen of the animals of the experimental group.

LDF («Transonic Systems Inc.»device, model BLF21) and TCM-2 Radiometer transcutaneous oxygemometer (Denmark). The analysis of the dynamics of microcirculation parameters in the skin of the abdomen of the control animals revealed a direct dependence of the level of PO2 on the parameters of microcirculation (with an increase in microcircula-

tion – intradermal PO2 increased, too). In the systematic running load the indicator of the microcirculation in the skin of the abdomen of the animal increased up to 10 days. Then, by the 30th day there was a decrease in the index of microcirculation. But in all cases it was higher than in animals of the control group. The level of intradermal PO2 was inversely related to the parameters of microcirculation determined with LDF. In animals of the experimental group there was a decrease in the level of PO2 in all cases compared to the control group.

It should be noted that the study of hemodynamic parameters of experimental animals by the methods described above is a promising area of modern physiology. The main advantages of using these non-invasive methods of research are: the possibility of repeated use in the experiment; the implementation of dynamic control over changes in the studied parameters.

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BRAIN PATHOLOGY IN SCHIZOPHRENIA: ASSOCIATION WITH CLINICAL AND CONSTITUTIONAL FACTORS

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ABSTRACT

Aim of study: to find the conjugation between pathological changes of schizophrenia patients brain structures, clinical picture of the disease and its constitutional and morphological features.

Materials and methods. 38 schizophrenia patients with schizophrenia with duration of disorder not less than 1 year and whose condition satisfied the diagnostic criteria of IDC-10 were under study. The study included magnetic resonance imaging, anthropometry, PANSS psychometric evaluation, registering basic clinical signs with hereditary burden, duration of disorder, the main symptoms. The criteria for not including were presenting marked deviations in physical investigation and neurological status, concomitant presence of traumatic brain injuries in anamnesis and other organic disorders, congenital and acquired pathologies of the skeleton system. The investigation participants' mean age was 39.5±11.7 years. Statistics was made using correlation analyses and Mann-Whitney criteria.

Results. The study shows that cysts and dyscirculatory foci are observed more often (14 patients, 36.8%, $p<0.05$) at negative disorders than at a positive domain. In subgroup of patients having prevalence in negative symptoms was found a direct correlation between constitutional-morphological type of patients and the expansion of the big brain hemispheres subarachnoid space ($p<0.05$), and opposite correlation between Tanner indexes and expansion of the cerebellum subarachnoid space ($p<0,05$). It was also found the direct correlation between cysts existence and constitutional-morphological type of patients ($p<0.01$) and the opposite correlation with Rees-Eysenk indexes.

Conclusion. Associations were found between morphological brain pathology, body constitution and clinical manifestations; they display the role of phenotype schizophrenia indications. The study shows that cysts and dyscirculatory points are observed more often at negative disorders than at a positive domain. It may be connected with disontogenesis impact on severity of schizophrenia. There were also found the association between hyperstenic somatotype, increasing of big brain hemispheres subarachnoid areas and gynecomorphy with the expansion of the cerebellum subarachnoid space. The results are important for testing the hypothesis about correlations between brain pathology and clinical and constitutional features of patients with schizophrenia.

Keywords: schizophrenia, negative symptoms, brain morphopathology, MRI, constitutional-morphological type.

Introduction. Current trends in scientific research of complex, multifactor phenomena increasingly consist in attracting interdisciplinary approaches to their study. Schizophrenia is a multifactorial problem and its decision is still intractable using only psychiatric methods. One of possible decisions of this problem could be the attraction of these approaches, which can integrate possibilities to study the morphofunctional unity, taking into account unsuccessful endeavors to find pathognomonic body changes for this disorder as a whole that could be verified by laboratory and instrumental methods, generally acknowledged in medicine.

One of the approaches in study of mental and behavioral disorders is constitutional, namely integrative-anthropological approach [19]. And the most well founded from methodological positions classification, which is used in integrative-anthropological approach, is the three-dimensional classification of constitutional-morphological types.

Besides the somatotype characteristics of patients with schizophrenia, one of good developed clinical anthropometry division is the verification of somatic sex maturation and dysplastic constitution types' [14], which have their own impact on disease process. At the same time, special importance is attached to regional morphological dysplasias, which reflect the dysontogenesis and serve as a factor of unfavorable schizophrenia prognosis [19]. Taking into account a fact that most of morphodysplasias are localized in cranium area [5], the brain morphopathologies investigation, which in fact can find small brain tissue anomaly, are attached the special importance.

As long ago as in the middle of previous century there was a question about one or another small anomaly to certain schizophrenia subtypes. So V.M. Mikhlin [16] found big number of cranium dysplasias using craniography of patients with schizophrenia, and its origin reasons he explained the pre-natal pathology. With making contrast X-ray investigation of 20 sick people and 24 couples of their relatives it was pointed that patients with simple or paranoid forms of the disorder had the size increasing only of third and side ventricles and subarachnoid gaps. Later M. Zapletálek et al. [4] found strong atrophic brain changes at schizophrenia with prevalent negative symptoms, T.K.A. Roberts [21] found brain ventricles extension in patients with schizophrenia with cognitive disturbances, negative symptoms and chronic course of disorder. N.C. Andreasen et al. [2] и T.J. Crow [7] found that the patients with positive and negative symptoms have neuromorphological structural differences, for example, the most frequent brain ventricles expansion have patients with negative symptoms. It appeared to be a neurobiological confirmation of dichotomic schizophrenia hypothesis and contributed the development of the dimensional approach. But in more later comparative studies [9, 23] it was demonstrated that neuromorphological anomalies in different schizophrenia subtypes have no differences. When non-invasive morphological imaging (computed tomography, magnetic resonance imaging) was originated, patients with schizophrenia comparing with healthy volunteers were observed temporal and frontal lobes changes in the form of a decrease in the volume and density of the white matter, as well as in other brain structures, in particular corpus callosum, caudate nucleus, parietal and occipital lobes. During all period of the disease for the patients brain volume decreasing and ventricles volume increasing together with grey matter decreasing is observed, mostly in frontal cortex, thalamus and cerebellum [1, 10]. Most often patients with schizophrenia have widenings of brain ventricular system and subarachnoid spaces, and different disorders of the vascular system: vascular cysts, dilated perivascular spaces, congenital arterial anomalies and impaired venous circulation signs [2, 17]. This vascular anomaly represents both functional and anatomical pathology of cerebral blood circulatory system and mark the current neurodegenerative process and congenital developmental

disorders. So, these and any other studies focus on searching the possible brain schizophrenia substrate or its particular clinical manifestations, but nevertheless there is no research works about the connection of brain pathology and constitutional features of the patients.

The aim of study is to find the conjugation between pathological changes of schizophrenia patients brain structures, clinical picture of the disease and its constitutional and morphological features.

Materials and methods. A morphometric analysis of brain magnetic resonance imaging of 38 patients with schizophrenia who were treated in the Department of Endogenous Disorders Clinic of the Institute of Mental Health was conducted. Europeoid race participants at the age from 18 to 60 years, who have the sickness catamnesis duration at least than 1 year, whose condition at the time of examination satisfied the diagnostic criteria for schizophrenia according to ICD-10 and who were able to give written informed consent, were included in our investigation. Criteria for not including were presence of explicit abnormalities during physical investigation and neurological status, presence of concomitant brain injuries or other organic pathology in anamnesis, congenital or acquired skeleton system injuries. Participants' middle age was 39,5±11,7 years.

According to the principles, accepted in clinical anthropology [19], anthropometric investigation was made according to the V. V. Bunak's methodic in V. P. Chtetsov's modification for adult samples [6] with counting Rees-Eysenk [20], Tanner [3] indexes, for constitutional-morphological types identification (hyposthenic, mesosthenic and hypersthenic) and somatic sex maturation (andromorphy, mesomorphy and gynecomorphy). Neuroimaging was made using MRI which was carried out using a Siemens MAGNETOM Avanto MRI scanner (Germany) 1.5 T in axial and sagittal projections (T2 and T1 weighted spin echo images). The investigation started with standard T2 weighted spin echo images to exclude pathological brain structure changes. A 3D-T1 gradient echo study mode (T1-mpr) was made for anatomical data obtaining with reception a set of slides (slice thickness 1.0 mm). Next sequentially it was received 4 sets of functional data (for each paradigm) in the T2*-gradient echo mode in axial projection (slice thickness 3.0 mm).

Taking into account previously obtained data about association of body build and schizophrenia symptoms leading clinical profile connection [13] and known data about inauspicious course of the disease with dominant negative symptomocomplex [26], the subgroup of patients was divided, who had negative symptoms on the foreground of clinical picture. This subgroup had PANSS verification [12]. These patients had 28,8±6,6 points for negative symptoms severity against 13,9±3,3 points for positive symptoms severity, general score was 84,1±14,9 points. This subgroup consists of 14 patients (36,8%), and they additionally were made a matching of brain MRI with their main constitutional characteristics.

Statistics were made with Statistica 8.0. The Mann-Whitney criteria was used to evaluate the significance differences in quantitative indicators. The Spearman's correlation coefficient was calculated for evaluation of the linear dependence of quantitative data. The obtained data during analysis for the values of the correlation coefficient r=0,5-1,0 with the significance level of differences p<0,05 were accepted as reliable ones.

The study was made according to the protocol, accepted by local ethical committee of the Mental Health Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Results and discussion. Morphometric analysis of schizophrenia patients' brain MRI showed correlations with some clinical-dynamical indexes: the hereditary burden, disorder duration, leading PANSS symptoms (Table 1).

A connection was found at p<0.05 between the leading domain in the positive/negative symptoms dichotomy framework and the either absence or presence of brain dyscirculatory foci. If the negative disorders prevail in the clinical picture the dyscirculatory foci are observed more often than with positive symptoms. Their appearance has a typical morphological pattern, revealed by magnetic resonance imaging (Fig.).

As the picture shows, the expansion of perivascular spaces and single dyscirculatory foci up to 2-5 mm are visualized in the white matter supratentorially and in the area of the brain legs. Also important is that the patient has brain ventricles extension in their intact form. Their body sizes are 9-10 mm. The third ventricle's size is 12 mm. In the periventricular zones edema is determined. In addition, there was revealedan intermediate sail cyst 23x8 mm. Cerebellum subarachnoid space is extended irregularly. The large brain convexital furrows are deepened a few. The pituitary gland is flattened. Another pronounced brain changes were not found. A bilateral nonexudative sinusitis is a contributing factor.

This picture of patient's brain MRI with negative abnormalities in the foreground illustrates the connection of symptoms with the dyscirculatiory foci presence.

The established dyscirculatory diturbances can be a reflection of the dystrophic and degenerative processes in the brain associated with the disorder. According to neuroimaging data these disorders are recorded more often for schizophrenia patients with severe negative symptoms [2] and combined with liquordynamics and all components of the cerebral circulation disturbances. They can also be attributed to dysontogenesis manifestations, which, as we have already mentioned above, are more often observed in more severe schizophrenia course with the persistent negative symptom complex development. This data confirm previous investigation results, that showed that MRI signs of brain abnormalities in schizophrenia are associated both with the current pathological process and have inborn features [22, 24].

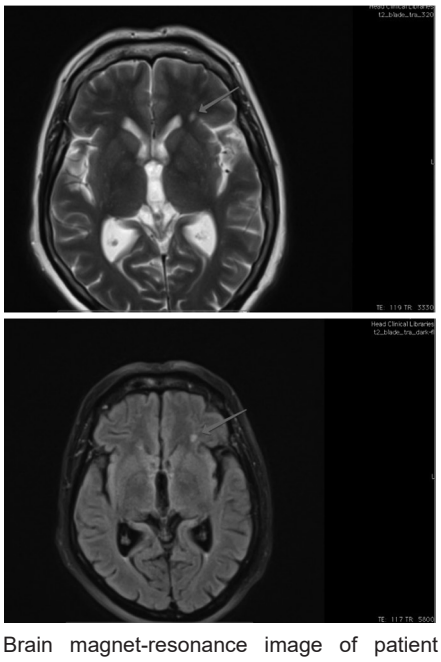
Besides, the brain dyscirculatory dis-

Table 1

Correlation between schizophrenia patient's brain mri with basic clinical-dynamical indexes

MR-parameter	Clinical-dynamical indexes		
	HB	DD	LS
The presence of dyscirculatory foci	–0,0350	0,2691	–0,3549*
Ventricular expansion	0,1178	–0,1994	0,0948
The symmetry of the lateral ventricles	0,1130	–0,2317	0,3013
Left lateral ventricle size (mm)	0,0646	0,1199	–0,0814
Right lateral ventricle size (mm)	0,1303	0,1491	–0,0248
The third lateral ventricle size (mm)	0,0260	0,2941	–0,1716
Periventricular edema	0,2639	0,1997	–0,0781
Subarachnoid space of the big hemispheres	–0,0434	0,1236	–0,0686
Subarachnoid space of the cerebellum	–0,0073	–0,1050	–0,1250
The presence of cysts	–0,0544	0,0712	0,0260

Note: * data with significance p<0,05; HB – hereditary burden; DD – disorder duration; LS – leading symptoms (positive/negative).



Brain magnet-resonance image of patient Ch., female, 55 years old, with schizophrenia negative domain.

turbances in patients with schizophrenia can be caused by long period antipsychotic drugs reception, which reduce the blood pressure, but there is a data [8], that by additional magnet-resonance investigations the vascular pathology features were also discovered by both first-sick patients and patients who had irregular antipsychotic therapy. In previous study [17, 25] in 10% patients with schizophrenia were identified brain development abnormalities, correlated with brain stem, cerebellum and pituitary and with hemodynamic disorders at these brain areas, blood flow decreasing at the dorsolateral cortex of schizophrenia patients with a leading negative symptomocomplex, and other neuromorphological disorders, predominantly the expansion of the brain ventricles with the decreasing of its weight and longitudinal size.

Taking into account previously explicated data a morphometric analyses of schizophrenia patients' brain MRI with negative disorders prevalence according their basic constitutional characteristics was made (Table 2).

Within the subgroup of patients with leading negative symptoms, there were found significant associations between the brain magnetic resonance imaging data and the main constitutional morphophenotype indexes. Particularly, a direct correlation was found between the patients' constitutional-morphological type and the expansion of the big hemispheres subarachnoid space ($p<0,05$) and the reverse correlation between the Tanner index and the expansion of the cerebellum subarachnoid space ($p<0,05$). These found correlations represent that the morphophenotypical shift towards hypersthenia in a negative symptom complex of schizophrenia is associated with an extended subarachnoid space in the cerebral hemispheres. The shift of somatic sexual maturation to gynecomorphy in this domain is associated with the expansion of the cerebellum subarachnoid space. A direct correlation between the presence of cysts with a constitutional-morphological type ($p<0,01$) and the reverse with the Rees-Eysenk index ($p<0,001$) shows that for people of hypersthenic body type with negative symptoms complex the formation of cysts is more characteristically. For the examined patients, they were located in the cortex and the white matter of the left frontal lobe, on the anterior of the left temporal lobe surface, on the convexital of the right temporal lobe surface, in the posterior cranial fossa, intermediate sail, in the cerebellum left hemisphere. At the same time, the localization of cysts, typical of a negative symptom complex, being confirmed at the level of statistical regularities, was not found.

Table 2

Correlation between schizophrenia patients' brain mri with negative disturbances prevalence and their basic constitutional characteristics

MR-parameter	Constitutional characteristics		
	I R-E	KMT	I T
The presence of dyscirculatory foci	–0,2314	0,4341	–0,0927
Ventricular expansion	0,2595	–0,3410	0,1738
The symmetry of the lateral ventricles	–0,0276	–0,0976	0,2375
Left lateral ventricle size (mm)	0,0324	–0,1941	0,1915
Right lateral ventricle size (mm)	0,2556	–0,1920	0,0147
The third lateral ventricle size (mm)	0,2242	–0,0990	–0,2097
Periventricular edema	0,2824	–0,0941	–0,4817
Subarachnoid space of the big hemispheres	–0,4153	0,5630*	0,1093
Subarachnoid space of the cerebellum	0,1636	–0,0296	–0,0690*
The presence of cysts	–0,8354***	0,7233**	0,2450

Note: * data with significance $p<0,05$; ** represents data with significance $p<0,01$; *** data with significance $p<0,001$; R-E I – Rees-Eysenk index; CMT – constitutional-morphological type; T I – Tanner index.

Conclusions. The collected data represent the cysts and dyscirculatory foci are observed more often with negative disturbances than with positive domain. This can be associate with dysontogenesis impact on schizophrenia severity. Also, the correlation was found between hypersthenic somatotype and expanding of the subarachnoid space of big brain hemispheres and gynecomorphy with cerebellum subarachnoid space expanding. The results of the study represent the role of constitution in schizophrenia clinical dynamics, they show its role with brain pathology and can be basis of early prognose for negative disorders. Due to opportune proper treatment it can help to improve care efficacy for this disorder.

This study is limited by using standard MRI for routine clinical practice. Lately, patients with schizophrenia are mainly examine with the functional MRI [18]. In addition, great emphasis is placed for longitudinal neuroimaging studies to identify the dependencies of these brain changes during treatment by various modern antipsychotics [11], and also during the remission formation [15]. However, our results are important for testing the hypothesis about the relationship of cerebral pathology with clinical and constitutional features of patients with schizophrenia.

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ANTIOXIDANT ACTIVITY OF A ADAPTOGENIC PLANT REMEDY IN MODEL SYSTEMS *IN VITRO*

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ABSTRACT

The antioxidant activity of the dry extract from the complex plant remedy has been studied in model systems *in vitro*. The complex plant remedy includes the following species of medicinal plants: *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench. It has been established that the plant remedy under study inhibits the oxidation of the biological substrate preventing from the destruction of β – carotene (IC_{50}=24.3 μg/ml) and yolk lipoproteids (IC_{50}=65.8 μg/ml) and having membrane stabilizing effect in peroxide (IC_{50}=0.97 μg/ml) and osmotic hemolysis (IC_{50}=0.11μg/ml) of erythrocytes. The complex remedy manifests the radical binding activity for 2,2-diphenyl-1- picrylhydrazyl (DPPH˙) (IC_{50}=61.4μg/ml), superoxide anion-radical (IC_{50}=28.6 μg/ml), nitrogen oxide (IC_{50}=55.3 μg/ml), also for Fe^{2+} (IC_{50}=639.3 μg/ml). The marked antioxidant activity of the tested remedy is due to the complex of biologically active substances (flavonoids, tannins, polyphenolic compounds, phenol carbonic acids, ecdysteroids, etc.) contained in its components.

Keywords: plant remedy, adaptogens, *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench., membrane stabilizing activity, 2.2-diphenyl-1- picrylhydrazyl, superoxide anion-radical, nitrogen oxide.

Introduction. Adaptation providing the body balance control in response to the changes in the external and internal environment is one of the main properties of living beings. The decline in adaptive skills or overstrain of adaptation mechanisms caused by pathogenic affects results in the development of pathological states due to the dysregulation of adaptive mechanisms manifested as so named "civilization diseases". Among dysmetabolic and desadaptative pathologies are: chronic heart insufficiency, cerebral circulatory insufficiency and especially the combination of the heart and brain vessel pathologies, dysfunction of central and peripheral neuroendocrine systems [17; 16]. To increase the resistance of the body to adverse health impact the various groups of medicinal means are used; among them adaptogens having the wide spectrum of pharmacological effects and increasing the resistance of the body to adverse exposure are commonly used. Their capability to regulate the hormone-mediated influence and lipid peroxidation plays a leading role in the mechanism of their effect [15; 19].

In this connection, it seems advisable the use of adaptogens of plant origin which have a systemic action on the body manifesting antioxidant, anti-inflammatory, psychotropic, cardio-protective and other effects due to the synergism of biologically active substances [6; 7; 17; 18; 19].

At the Institute of General and Experimental Biology SB RAS the dry extract has been derived from the complex plant remedy consisting of the aerial part of *Serratula centauroides* (L.), leaves of *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench. Previous experiments have shown that the given complex plant remedy has the marked actoprotective activity increasing physical endurance in rats due to optimization of the energy metabolism [2], as well it manifests anti-stress and anti-depressive effects in chronic stress [9].

The aim of the study is to estimate the antioxidant activity of the adaptogenic plant remedy in model systems *in vitro*.

Material and methods of investigation. The subject of the study was the complex plant remedy in the form of the dry extract consisting of *Serratula centauroides* (L.), *Bergenia crassifolia* (L.) Fritsch, *Rosa davurica* Pall., *Inula helenium* L., *Echinacea purpurea* (L.) Moench.

The method of the dry extract obtaining involves the extraction of the powdered plant material by 30-70% ethyl alcohol, concentration and drying in the vacuum set [12].

The membrane stabilizing activity of the tested remedy was estimated in the models of peroxide and osmotic hemolysis with the 1% erythrocyte suspension (Er/m). The peroxide hemolysis of erythrocytes was induced by Fenton reagent [22] and osmotic hemolysis – by adding of the distilled water into the incubation medium [4]. The tested plant

remedy was studied in 0.01; 0.1; 1.0; 10; 100 and 500μg/ml concentrations. Ascorbic acid (*Sigma Aldrich, USA*) was used as a preparation of comparison in final concentrations: 0.0002; 0.001; 0.01; and 0.5 μg/ml. The specimens were analyzed in the spectrophotometer at the 540 nm wavelength. The membrane stabilizing effect of the tested remedy and the preparation of comparison was estimated in percentage terms in regard to the indices in the control (incubation medium free of the dry extract).

The antioxidant activity of the tested remedy was estimated according to the level of its influence on the dynamics of peroxide destruction of β-carotene (PDBC) in the DMSO-H_2O_2-oleic acid system [15]. The influence of the plant extract on the process of protein metal-catalyzed modification was studied in the model biological system (MBS) of yolk lipoproteids (YLP) [8]. The antiradical activity was estimated in regard to the stable radical 2.2-diphenyl-1- picrylhydrazyl ($DPPH^{\cdot}$) [14]; in regard to superoxide radicals ($O_2^{\cdot-}$) in the nonenzymatic system phenazine methosulfate/NADN [21]; also in regard to NO molecules [21]. Fe^{2+}-chelating activity of the dry extract was determined with the use of o-phenanthroline method [13]. Quercetin, rutin, arbutin and ascorbic acid were used as substances of comparison (*Sigma Aldrich, USA*). All *in vitro* experiments were carried out in three replications. The means of the data obtained were expressed in terms of concentration required for binding 50% reactive particles in the incubation medium (IC_{50}). The data obtained were processed statistically according to recommendations [3].

Results and discussion. The research has shown that the dry extract of the complex plant remedy has the marked membrane stabilizing activity *in vitro* experiments (Table 1). Inclusion of the tested plant extract into the incubation medium decreased the intensity of OH-mediated oxidation of the erythrocyte plasma membrane. The concentration of the extract in the incubation medium up to 500μg/ml was followed by increasingly membrane stabilizing activity. Further strengthening of the tested remedy resulted in the plasma membrane rupture and denaturation of hemoprotein (the data are not presented). The concentration of the dry extract inducing 50% inhibition of the peroxide erythrocyte hemolysis process was 0.97μg/ml. Besides, the complex remedy when interacting with the erythrocyte plasma membrane promoted its permeability in hypotonic conditions resulting in the decrease of osmotic hemolysis intensity (IC_{50} = 0,11μg/ml). The revealed action of the tested plant remedy is due to the membrane stabilizing effect of the plant components presenting in its content: *S. centauroides, B. crassifolia, R. davurica* which are rich in polyphenolic complex, tannins and flavonoids having the membrane stabilizing effect [5; 10].

The data given in the Table 2 have shown that the complex plant remedy has the marked antioxidant properties preventing β-carotene from the peroxide destruction (IC_{50} = 24.3μg/ml) and inhibiting the degradation of lipoproteins in metal-catalyzed oxidation (IC_{50} = 65.8μg/ml). The activity of the tested remedy in the given model systems was comparable with the substance of comparison – arbutin.

It has been established that the dry extract has the marked antiradical effect (Table 3). The tested remedy manifests activity in respect of DPPH molecules that is due to the presence of phenolic compounds in its content. The value of DPPH 50% binding by the plant remedy was 61.4 μg/ml which surpassed the same index for the substance of comparison – arbutin.

The experiments for the evaluation of the tested remedy capacity to bind the active forms of oxygen ($O_2^{\cdot-}$ and NO) and mixed valence metals have revealed its antiradical activity in regard to the given reactive particles. The complex plant remedy manifests the marked Fe^{2+}-chelating activity (IC_{50}=639.3 μg/ml) which is higher than in quercetin, rutin and arbutin (Table 3).

The tested plant remedy interacts with $O_2^{\cdot-}$-radical more intensively in the *in vitro* model system than ascorbic acid and arbutin (IC_{50} = 28.6μg/ml). $O_2^{\cdot-}$-binding activity of the complex remedy is comparable with quercetin (IC_{50} = 31.2μg/ml). *In vitro* study has shown that the tested plant remedy manifests the marked activity in regard to NO molecules binding (IC_{50} = 55.3 μg/ml). The plant remedy surpasses quercetin and ascorbic acid trailing only the arbutin in this kind of activity.

Thus, the data obtained have demonstrated that the complex plant remedy has the marked antioxidant effect. The given activity is obviously due to the pronounced antioxidative activity of its components: *B. crassifolia* (hydroquinone, arbutin, dihydroquercetin, quercetin, rutin, gallic acid) [10]; *R. davurica* (quercetin, hyperoside, hyperin, gallic acid) [10]; *I. helenium* (quercetin, caffeic acid, scopoletin, umbelliferone) [11].The components of the complex remedy contain biologically

Table 1

Membrane stabilizing activity of the dry extract from the adaptogenic plant remedy in the model system *in vitro*

Subject	Concentration, μg/ml	Peroxide hemolysis, %	Osmotic hemolysis, %
Dry extract	500	11,25±0,33	6,70±0,14
	100	11,01±0,41	10,21±0,51
	10	36,91±1,24	28,60±1,62
	1	40,82±1,15	37,82±2,11
	0,1	49,27±3,10	50,23±2,45
	0,01	74,47±2,55	58,54±2,05
	IC50, мкг/мл	0,97±0,02	0,11±0,01
Ascorbic acid	0,5	27,89±1,12	10,57±0,43
	0,1	34,85±1,20	14,38±0,35
	0,01	48,86±2,31	24,80±1,10
	0,001	56,56±2,17	50,60±2,02
	0,0002	67,70±2,42	55,49±2,18
	IC50, мкг/мл	0,009±0,0003	0,002±0,0001

Table 2

Antioxidant activity of the dry extract from the adaptogenic plant remedy, IC_{50}

Subject	PDβC, μg/ml	MBS-YLP, μg/ml
Dry extract	24,3±2,11	65,8±3,17
Quercetin	10,2±0,29	16,2±1,34
Rutin	9,7±1,11	18,8±1,23
Arbutin	25,2±1,23	73,1±3,73
Ascorbic acid	9,1±0,42	39,3±2,12

Table 3

Antiradical activity of the dry extract from the adaptogenic plant remedy, IC_{50}

Subject	Reactive molecules			
	$DPPH^{\cdot}$, μg/ml	$O_2^{\cdot-}$, μg/ml	Fe^{2+}, μg/ml	NO, μg/ml
Dry extract	61,4±2,13	28,6±3,10	639,3±11,15	55,3±2,31
Quercetin	10,3±0,54	31,2±2,11	>5000	170,2±4,21
Rutin	15,1±1,13	2,3±0,15	>5000	15,3±1,12
Arbutin	105,4±2,71	>550	>5000	35,7±1,26
Ascorbic acid	4,8±0,15	91,3±3,22	110±6,42	975,0±27,13

active substances (flavonoids, tannins, polyphenolic compounds, phenol carbonic acids, ecdysteroids, etc) having the property to form phenoxy radicals, chelate mixed valence metal ions, bind OH and O_2 molecules it promotes stabilization and structural-functional reintegration of the plasma membrane [1].

In this connection the further study of the antioxidant activity of the given complex plant remedy *in vivo* experiments seems to be advisable.

Conclusion. 1. The dry extract of the adaptogenic plant remedy promotes preservation of the structural-functional integrity of the erythrocyte membrane in plasma membrane OH-mediated oxidation and osmotic injury *in vitro*;

2. The tested plant remedy manifests the marked antioxidant activity preventing from biomacromolecule oxidation in model systems;

3. The dry extract demonstrates the antiradical activity *in vitro* in regard to such reactive particles as 2,2-diphenyl-1-picrylhydrazyl, superoxide anion-radical, nitrogen oxide and Fe^{2+} ions.

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MORPHOFUNCTIONAL INDICATORS OF ORGANISM OF THE ATHLETES-WRESTLERS OF YAKUTIA

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ABSTRACT

The article is devoted to a comprehensive study of the physical development and physique of freestyle wrestlers, as well as functional parameters of the body. The indicators of cardiovascular system - dynamics of indicators of adaptive potential and coefficient of endurance of athletes in different seasons of the year are studied.

38 men of Yakut nationality, aged 18 to 29 years, athletes – freestyle wrestlers having high sports qualification were the **object** of our study. The comparison group was 20 male cadets of the police school. The compared groups were comparable in age. The study was conducted in different seasons: summer (June), autumn (October), winter (December), spring (March).

We revealed that, among highly qualified wrestlers Yakut nationality, dominated the brachymorphic somatotype, characterized by an average or low growth, relatively long torso, broad shoulders, a large breast, short lower limbs. Analysis of the data showed that 34.2% of the athletes surveyed by us were overweight, as well as high values of the Rohrer index. Low heart rate values are probably a sign of adaptation to intense physical activity. The increase in AP points indicates signs of CVS stress, which is associated with an increase in physical and psycho-emotional stress in the autumn due to the beginning of the annual cycle of training, and in winter and spring with participation in competitions of various levels. The increase in EC (> 16.e.) 10% -18% of the surveyed us freestyle wrestlers indicates the voltage of the myocardium, and decrease in EC (< 12 e.) 45% -55% may be a sign of exhaustion of the myocardium.

Keywords: athletes, cardiovascular system, blood pressure, adaptive potential, coefficient of endurance.

Adaptation is one of the basic concepts in physiology. In the Far North, the adaptation of the human body to the conditions of habitat in high latitudes takes a special place and is provided by the restructuring of all body systems. The harsh climate also affects anthropometric indicators. T.I. Alekseeva [1], describing the «Arctic» adaptive type, indicates such features of the physical constitution of the indigenous population as a small body length, relatively wide chest, muscular body type, high body density. G.K. Stepanova [12] notes that the comparative analysis of the study of the dynamics of anthropometric data for 20 years showed that the growth in the population of young Yakuts significantly increased, but was not accompanied by the addition of body weight. This is consistent with the data of S.P. Permyakova [5] and V.G. Starostin [8] who noted an increase in the dolichomorphy among the indigenous peoples of the North and a decrease in the prevalence of representatives of the brachymorphic somatotype over the same period of time.

The human circulatory system is responsible for the adaptation of the body to various environmental factors. In most cases, the cardiovascular system (CVS) can be considered as an indicator of the body's adaptation. The study of CVS reactions allows to measure the level of functioning of the circulatory system, such as minute and shock blood volume, pulse rate, blood pressure, as well as to calculate such integrative indicators as the adaptive potential (AP) and endurance coefficient (EC) of CVS. Under excessive physical exertion in extreme Northern conditions, there are adaptive changes in athletes CVS, change in hemodynamic parameters. Adaptation to physical activity is accompanied by an increase in the impulse of the heart. The increase in the impulse of the heart affects the pulse at rest, it becomes much less frequent [6, 9 -12].

The aim of the research was to study the morphometric parameters of physical development and evaluation of the functional state of the body of freestyle wrestlers of Yakutia.

Materials and methods of research. The object of our study were 38 men of Yakut nationality, aged 18 to 29 years, athletes – freestyle wrestlers of School of the highest sports skill of Yakutsk and students of the Institute of physical culture and sports M.K. Ammosov NEFU having high sports qualification: candidates for masters of sports, masters of sports, masters of sports of international class, honored masters of sports. The comparison group was composed from 20 male cadets of the Yakutsk police school attending classes in general physical training. The compared groups

were comparable in age. The study was conducted in different seasons: summer (June), autumn (October), winter (December), spring (March).

We calculated body mass index (BMI) or Quetelet index and Rohrer index, which is used as a group growth-weight index.

The main indicators of the functional state of the CVS, which determine the development of adaptation of the body, include heart rate (heart rate), all types of blood pressure (systolic (SBP), diastolic (DBP)) and pulse (PP) (the difference between the ratio of systolic and diastolic pressure).

Among the numerous criteria proposed for assessing the functional state of compensatory-adaptive mechanisms that provide adaptation and homeostasis of the body under the effects, often having a stressful character, an important role belongs to the definition of AP of the circulatory system, reflecting in conventional units – points the degree of tension of adaptation mechanisms, manifested in changes in hemodynamic parameters. AP organism was calculated by the formula: AP=0,011PR+0,014SBP+0,008DBP+0,014A+0,009BW–0,009G–0,27, where PR – pulse rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; G – growth; BW – body weight; A – age. Scale of assessments for the indicator AP: 4 points-2.10-satisfactory adaptation (characterizes sufficient functionality of the circulatory system); 3 points - 2,11-3,20 - functional stress adaptation mechanisms; 2 points - 3,21-4,30 - unsatisfactory adaptation (characterizes the decrease in the functionality of the circulatory system with insufficient, adaptable reaction to the loads); 1 point - more than 4.30 - destruction of adaptation (characterizes a sharp decrease in the functionality of the circulatory system with the phenomenon of failure of the mechanisms of adaptation of the whole organism) [2].

EC characterizes the functional state of the CVS and is an integral value that combines the heart rate with pulse pressure [3]: calculated by the Kvas formula: EC = HR x 10/PP. Normal EC from 12 to 16.e.

The data obtained were statistically processed using the SPSS 17.0 statistical software application package. For all indicators in each group, the arithmetic mean values (M) and the errors of the mean values (m) were calculated. The level of significance was considered significant at p≤0.05. The significance of the differences was determined using non-parametric Mann-Whitney criteria. The Spearman linear correlation coefficient was calculated to identify the conjugacy of the indicators.

Table 1

Anthropometric indicators of highly qualified freestyle wrestlers

Parameter	Freestyle wrestlers (n=38)	Control group (n=20)	p
Age, years	22,0 (22,0; 25,0)	24,0 (22,5; 25,5)	0,070
Height, m	1,7 (1,6; 1,7)	1,8 (1,7;1,8)	<0,001
Body weight, kg	62,5 (58,0; 72,0)	68,5 (66,0; 74,5)	0,010
The Rohrer's Index	14,7 (13,8; 17,2)	12,9 (12,0; 14,2)	<0,001
BMI, kg/m^2	23,7 (22,7; 26,0)	22,8 (21,3; 24,5)	0,062

Note. In the Tables 1-3 data are presented in the form of median and interquartile distribution in Me (Q1; Q3) format; p – achieved level of statistical significance of differences in comparison of groups (Mann-Whitney criterion).

Results and discussion. Body size (along with other indicators characterizing physical development) are important parameters of sports selection and sports orientation. Table 1 presents the results of anthropometric indicators of the men we examined.

When assessing the distribution of growth was considered undersized person with the growth of 167 cm and below average height – with the limits of growth 168-179 cm, and tall – 180 cm and above [12]. Analysis of the distribution of growth showed that there are significant differences between the groups (Figure 1). 61% of freestyle wrestlers were undersized athletes, while in the control group undersized was 5%. The share of tall was 13 and 30%, respectively. Thus, among the examined highly skilled freestyle wrestlers dominate undersized athletes, and among the persons constituting the control group was dominated by persons with a mesomorphic type.

Differences in BMI values did not reach the level of statistically significant, but in athletes both the median and the boundaries of quartiles were shifted towards larger values. The analysis of the data showed that 13 (34.2%) wrestlers were overweight, while in the control group the same figure was 4 (20%). This is probably due to the peculiarities of morphofunctional features (differences in the composition of the body, more muscle mass in athletes). Thus, the Rohrer index characterizing the body density was significantly higher in wrestlers than in the control group (p<0.001).

Indicators of the functional state of the CVS of the persons examined by us are given in the Tables 2 and 3.

According to our data, the heart rate in the group of athletes, depending on the season, did not change statistically significantly. However, athletes heart rate in all seasons was lower than in the control group. Thus, in comparison with the control group, athletes ' heart rate at rest in autumn was lower by 16% (p<0.01), in winter it did not change, and in spring it was lower by 14% (p<0.05). In the control group, depending on the season of the year, statistically significant differences in heart rate were revealed. Thus, there was a decrease in heart rate in winter and spring by 11% (p<0.05) and 8%, respectively, in comparison with the autumn season. Slowing of heart rate or bradycardia (45-60 beats per minute) was observed in summer in 33% of wrestlers, in autumn – in 54%, in winter – in 64% and in spring – in 40% (Table 2). Bradycardia, stated in some highly qualified athletes in all seasons of the year, may be a sign of heart hypertrophy under the influence of intense physical activity.

Due to the fact that the annual training cycle is divided into different stages, we analyzed the AP depending on the season of the year (Table 3). The analysis of AP revealed that the average AP scores in athletes during the year

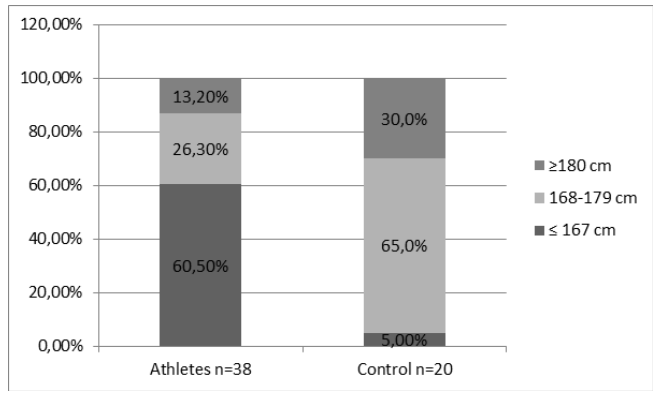

Fig. 1. Growth distribution in the compared groups

exceed 2.1 points, which indicates the stress of adaptation mechanisms, which is probably due to a decrease in heart rate. Since adaptation to physical activity is associated with an increase in the shock volume of the heart. While in the control group signs of stress adaptation mechanisms appear only in the spring.

In a more detailed analysis revealed that in the summer 39% of athletes AP was at the level of satisfactory adaptation, 61% - corresponded to the level of stress adaptation mechanisms. In autumn, the number of athletes with AP at the level of satisfactory adaptation decreased to 27%, while in the control group at this time of the year the level of satisfactory adaptation was noted in 87%. That is, the tension of adaptation mechanisms was observed in 73% of athletes, and in the control group only in 13%. In winter, satisfactory adaptation among athletes was observed in 43%, and among the control group – in 71%. In other words, the tension of adaptation mechanisms was observed in 57% of wrestlers, while in the control group – in 29%. In spring, both among athletes and among the control group, 40% were at the level of satisfactory adaptation, and 60% experienced tension of adaptation mechanisms.

Study EC in athletes depending on the season of the year showed that the highest average rates were observed in the summer of 13.32±2,89.e. and the lowest of 10.09±1,67.e. in the spring, indicating that the fatigue of the CVS (Figure 2).

The most favorable indicators of EC were noted in the spring, the greatest overvoltage of CVS was noted in the autumn, the greatest fatigue of CVS – in the summer. Our data indicate that intense physical and psychoemotional load, experiencing highly skilled athletes, affect the functional state of compensatory-adaptive mechanisms for adaptation and the degree of fitness of the CVS. At the same time, the greatest stress of adaptation mechanisms athletes experience in the autumn. Probably, this is due not only to the beginning of the annual cycle of training, but also the influence of climatic factors.

The increase in the number of wrestlers with signs of CVS stress to 73% is in the autumn due to the beginning of more intense physical activity after the summer period. In addition, the state of CVS athletes affected by climatic factors (in October, set a negative temperature to -20°C), reduced insolation (shortening of daylight hours), changes in atmospheric pressure. The increase in the number of athletes with satisfactory adaptation in winter (up to 43%), in spring – up to 40%, is likely due to the fact that athletes are gradually entering a certain training regime. However, the fact that 57% (AP 2,13 points) of wrestlers in the winter and 60% (AP 2,21 points) of wrestlers in the spring, have signs of tension of CVS that testifies that in these seasons of year they experience the greatest physical and psychoemotional loadings. Since the greatest number of different competitions falls on these periods.

The results of our research do not contradict the information given in the literature. In the few publications relating to structural and functional features of CVS athletes of Yakutia shows that intense professional sports can contribute to decompensatory changes of AP from individual athletes (group risk). This is manifested by an increase in the mass of the left ventricular myocardium, violations of hemodynamic parameters: higher blood pressure, bradycardia, while a higher total peripheral resistance, which indicates a violation of intrasystem interactions and the transition to myocardial hypertrophy (4, 6, 7, 9- 14].

Thus, in highly qualified wrestlers of the Yakut nationality, the brachymorphic somatotype dominated, characterized by an average or low growth, relatively long torso, broad shoulders, a large breast, short lower limbs. Analysis of the data showed that 34.2% of the athletes surveyed by us were overweight, as well as high values of the Rohrer index. Low heart rate values are probably a sign of adaptation to intense physical activity. The increase in AP points indicates signs of CVS stress, which is associated with an increase in physical and psycho-emotional stress in the autumn due to the beginning of the annual cycle of training, and in winter and spring with participation in competitions of various levels. The increase in EC (> 16.e.) 10% -18% of the surveyed us freestyle wrestlers indicates the voltage of the myocardium, and decrease in EC (< 12 e.) 45% -55% may be a sign of exhaustion of the myocardium.

Table 2

Indicators of the functional state of the cardiovascular system in freestyle wrestlers

Parameter	Freestyle wrestlers (n=38)	Control group (n=20)	p
SBP, mm	124,0 (119,0; 127,0)	122,5 (115,0; 128,0)	0,763
DBP, mm	73,0 (66,0; 79,0)	74,0 (67,0; 81,5)	0,587
HR, min	61,0 (54,0; 66,0)	69,0 (56,5; 74,0)	0,029
AP (N up to 2.1 points)	2,0 (1,7; 2,3)	2,2 (2,0; 2,4)	0,048
EC (N 12-16 e)	12,0 (10,4; 15,6)	14,2 (12,9; 15,6)	0,091

Table 3

IIIndicators of the functional state of the cardiovascular system in freestyle wrestlers in different seasons of the year

	Summer n=18	Autumn n=10	Winter n=17	Spring n=32	p
SBP, mm	125,5 (121,3; 130,5)	126,5 (121,8; 133,0)	122,0 (118,0; 128,0)	124,5 (115,0; 134,0)	0,058
DBP, mm	71,0 (63,5; 77,5)	74,0 (67,8; 83,5)	73,0 (66,5; 80,0)	74,5 (68,0; 82,0)	0,691
HR, min	62,5 (53,5; 67,5)	58,5 (51,3; 68,8)	59,0 (56,5; 63,0)	62,0 (52,0; 67,0)	0,308
AP	2,2 (2,0; 2,4)	2,2 (2,1; 2,4)	1,6 (1,5; 1,8)	1,7 (1,5; 1,9)	0,013
EC	11,4 (8,9; 15,3)	10,7 (7,6; 16,8)	12,6 (10,6; 14,9)	12,7 (10,2; 15,7)	0,308

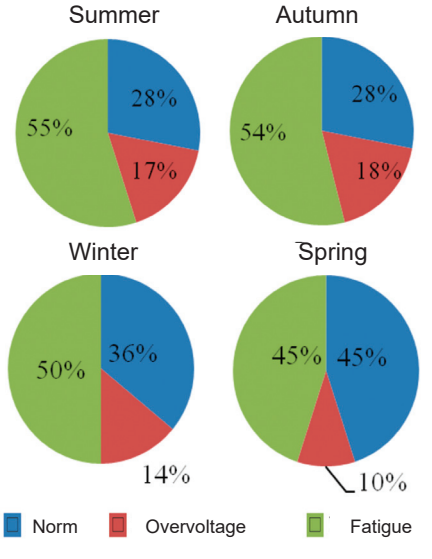

Fig. 2. Frequency of overvoltage and fatigue of CVS on EC in wrestlers depending on the season of the year (%)

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DIAGNOSTIC AND TREATMENT METHODS

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THE FIRST HUMAN HEART TRANSPLANT IN THE FAR EASTERN FEDERAL DISTRICT OF THE RUSSIAN FEDERATION

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ABSTRACT

The article describes a clinical case - the first experience of heart transplantation in a remote region of the Russian Federation with hard-to-reach settlements in extreme climatic and geographical conditions. The surgery was performed on July 6, 2018 in the city of Yakutsk, the Sakha Republic (Yakutia), the Far Eastern Federal District, the Russian Federation. Some data on the stages of the formation and development of heart transplantation abroad and in Russia are given. The preparatory stage for this surgery and the organization of the collection of the donor organ are described. Of the 95 patients with chronic heart failure with a decrease in the ejection fraction, 4 patients were selected for inclusion on a waiting list for heart transplantation. All patients were males with severe chronic heart failure with a functional grade III-IV according to NYHA classification. They had an expansion of the cavities and a decrease in the pumping function of the heart below 30%. Then clinical observation data are given. After a complete examination of the recipient, a clinical diagnosis was made: I42.0 Dilated cardiomyopathy. I48.1 Permanent atrial fibrillation, tachysystolic variant. I50.0 CHF 2B Stage, NYHA FC III. I34.0 Mitral valve failure grade 3. I36.1 Tricuspid valve failure grade 2. I27.2 Pulmonary hypertension grade 1. Details are given of the technique of donor heart removal surgery, explantation and heart transplantation. The features of the heart transplantation surgery in this clinical observation are indicated. The data of functional methods of research, the results of myocardial biopsy and coronary angiography of the transplanted heart in the postoperative period are presented. The patient was discharged on the 26th day after the operation, upon the examination after 4 months the state of health is satisfactory, there are no signs of heart failure or transplant rejection. Based on the results obtained, the possibility of implementation and the need to conduct such operations in remote regions of the Russian Federation are discussed.

Keywords: heart transplantation, first experience, Yakutia, Far Eastern Federal District.

Introduction. At present, heart transplantation is the main radical surgical method for treating terminal heart failure [4, 11]. According to the register of the International Society of Heart and Lung Transplantation (ISHLT), 4 to 5 thousand human heart transplantations are performed annually in the world [9]. The vast majority of these surgeries are carried out in Europe and North America (Fig. 1). In Russia in recent years, there has also been an increase in transplantation operations, including heart. The number of clinics where the HT is carried out has increased. So, in 2018, the first successful HT surgeries were conducted in the Altai Territory, the Southern Urals (Chelyabinsk), Rostov-on-Don and in Yakutsk. The number of completed HTs per year in the Russian Federation increased from 49 in 2009 to 220 in 2016 [2].

The first successful human heart transplantation was performed at the Groote Shuur Hospital (South Africa) in December 1967 by C. Barnard [8]. Despite the fact that the surgery was performed flawlessly, the patient lived for 18 days and died of bilateral pneumonia. The second heart transplantation (HT) was conducted in 1968 at Stanford University (USA) by the famous American heart surgeon N. Shumway - the author, who proposed the biatrial method of orthotopic heart transplantation (OTHT). The first transplantation operations were accompanied by a high degree of rejection of donor organs, thereby worsening the survival rate of the recipients. As a result, until the discovery of cyclosporine-based immunosuppression in 1980, the number of these operations was small. Immunosuppression significantly improved the results of transplantations, the number of heart transplantations increased [10]. However, there remain quite a lot of problems in the field of heart transplantation. In Russia, the first heart transplantations were performed by A.A. Vishnevsky (1968), G.M. Soloviev (1974), V.I. Burakovsky (1983), V.I. Shumakov (1986). Unfortunately, they were unsuccessful. In the national medical practice, the first successful heart transplantation was performed at the Federal Research Center of Transplantology and Artificial Organs and the Ministry of Health of the USSR by the Academician V.I. Shumakov in 1987 [7].

Transplantology in Yakutia began in 2001 with the transplantation of a kidney from a relative. After the first successful operations, the second stage in the development of transplantology in our republic was the transplantation of fragments of a related liver. As of July 2017, 82 kidney transplants and 7 liver frag-

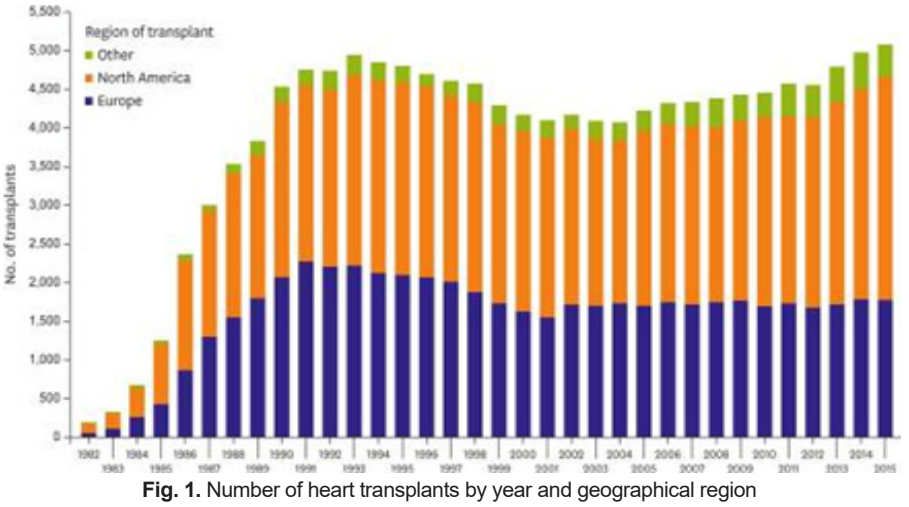

Fig. 1. Number of heart transplants by year and geographical region

ment transplants from a related donor were performed in the Republic of Sakha (Yakutia) [3].

Since 2016, a new stage in the development of transplantation in Yakutia has begun - this is the introduction of cadaver organ transplantation into clinical practice. Transplantations of the cadaveric kidney, fragments of the cadaveric liver, cadaver cornea were carried out [6]. All this was preceded by a great preparatory work.

The next task was the implementation of a heart transplantation. According to the chief transplantologist of the Russian Federation S.V. Gautier, the need for a heart transplant is met by only 22% [1]. The urgency of the HT problem in Republic of Sakha (Yakutia)) is due to the high incidence of circulatory system diseases among population, including chronic heart failure, due to coronary heart disease, previous myocardial infarction, dilated cardiomyopathy. Also, an important role in the development and aggravation of cardiovascular diseases is played by the natural and socioeconomic extreme conditions of life in the North. The inhabitants of the north are more likely than southerners to be exposed not only to colds, but also to cardiovascular diseases (CVD) [5]. It is well known that in order to perform a successful HT, the recipient must reside in the area where the clinic performing the HT is located, since at any moment a cadaveric donor organ may be collected. Based on the above, the importance of the development of transplantology in regions with large multidisciplinary medical centers with the ability to perform organ transplantations is obvious.

The purpose of our message is the implementation of the first successful HT in the Far Eastern Federal District of the Russian Federation. The surgery was performed on July 6, 2018 with the participation of two leading clinics of the city of Yakutsk, the Republic of Sakha (Yakutia): Republican Hospital No. 1 - the National Center of Medicine and the Republican Hospital No. 2 - the Center for Emergency Medical Aid.

Clinical observation. Before the implementation of the HT in the Republican Hospital No. 1 - the National Center of Medicine, the first stage was a large organizational and methodological work, equipment was purchased, specialists were trained, a waiting list of the donor heart was formed. We selected 4 people from 95 patients suffering from chronic heart failure with a decrease in the pumping function of the heart of various degrees on the waiting list of the donor heart. Among the selected patients, two suffered from coronary heart disease with the development of ischemic cardiomyopathy and two were with dilated cardiomyopathy. All of the patients were males with severe chronic heart failure with a functional grade III-IV according to NYHA classification. There was an expansion of the cavities and a decrease in the pumping function of the heart below 30%.

Patient A., 58 years old, was admitted to the RH#1 - NCM with complaints of shortness of breath at the slightest exertion, sometimes at rest, feeling of lack of air, general weakness, decreased tolerance to physical exertion, pressing pain in the region of the heart, dizziness.

From the anamnesis, it is known that for the first time an enlargement of the heart was detected on a planned fluorography in 2009, but the state of health was relatively satisfactory and the patient did not undergo further examination. Since 2014, the patient had been experiencing shortness of breath and periodic pressing pain in the heart with moderate physical exertion. A sharp deterioration of health and a decrease in tolerance to physical exertion had been noted since 2016. The patient was examined in the Republican Cardiology Clinic: dilatation of the heart chambers and atrial fibrillation were detected, and conservative treatment with dynamic observation was recommended. In 2017, he was hospitalized in the cardiac surgery department of RH#1 for further examination and deciding on HT necessity.

The examination of the patient showed negative dynamics. According to echocardiography (EchoCG), there was an increase in all chambers of the heart with a left ventricular end diastolic diameter of 7.1 cm (end diastolic volume 220 ml), end systolic diameter of 5.5 cm (end systolic volume 176 ml). There was also a significant decrease in myocardial contractility with diffuse left ventricular hypokinesis (ejection fraction using Teichholz formula — 22%, Simpson's formula — 20%), mitral valve insufficiency of grade 3, tricuspid valve insufficiency of grade 2. The calculated systolic pressure in the right ventricle was 29.1 mm Hg. According to coronary angiography and left ventriculography, moderate atherosclerotic lesions of the coronary arteries without hemodynamically significant narrowings, diffuse hypokinesis of the left ventricular myocardium were detected.

After a full examination, a clinical diagnosis was made: I42.0 Dilated cardiomyopathy. I48.1 Permanent atrial fibrillation, tachysystolic variant. I50.0 CHF 2B Stage, NYHA grade III. I34.0 Mitral valve failure of 3 degree. I36.1 Tricuspid valve failure of 2 degree. I27.2 Pulmonary hypertension grade 1.

Taking into account the progression of heart failure and the ineffectiveness of conservative treatment, as well as on the basis of the results of laboratory and instrumental examinations, the patient was offered orthotopic heart transplantation (OTHT). Consent was obtained, the patient was included in the waiting list for OTHT.

On July 6, 2018, an orthotopic heart transplantation was performed.

In our republic, the clinic where a donor's brain death is determined, followed by removal of the cadaveric organs, is Republican Hospital No. 2 - the Emergency Medical Center, which provides emergency medical care throughout the Sakha Republic (Yakutia). When performing the collection of donor organs, coordinated joint work is carried out between the two republican hospitals. Removal of the donor heart was carried out simultaneously with other surgical teams using the method of multiorgan organ removal (heart, liver, kidney).

For the donor heart collection, the technique recommended by the Federal Research Center for Transplantology and Artificial Organs named after Academician V.I. Shumakov (Fig. 2A) was used.

After pericardiotomy, a visual and palpatory assessment of the donor heart was performed. Then the aorta and the pulmonary artery were mobilized. In the next stage the superior vena cava (SVC) was dissected free from the surrounding tissue high before the bifurcation with the nameless vein and harnessed by dacron, then the inferior vena cava (IVC) was dissected from the surrounding tissue. Incisions were made on the pericardium next to the IVC, for subsequent convenient clamping with a clamp. After systemic heparinization (5000 U), the ascending aorta was cannulated at a high level. The SVC was tied up with dacron, a clamp was fixed on the IVC at the level of the diaphragm with its intersection at ½. The inferior pulmonary vein was cut for decompression of the left sections. Then the ascending aorta was clamped and antegrade cardioplegia was began with a cooled solution of custodiol (3 liters) with simultaneous external cooling of the heart with crumbled ice. The pericardium was widely opened to better evacuate the preservative solution into the pleural cavity. Removal of the heart was completed by cutting off the IVC, all pulmonary veins, aorta, pulmonary arter-

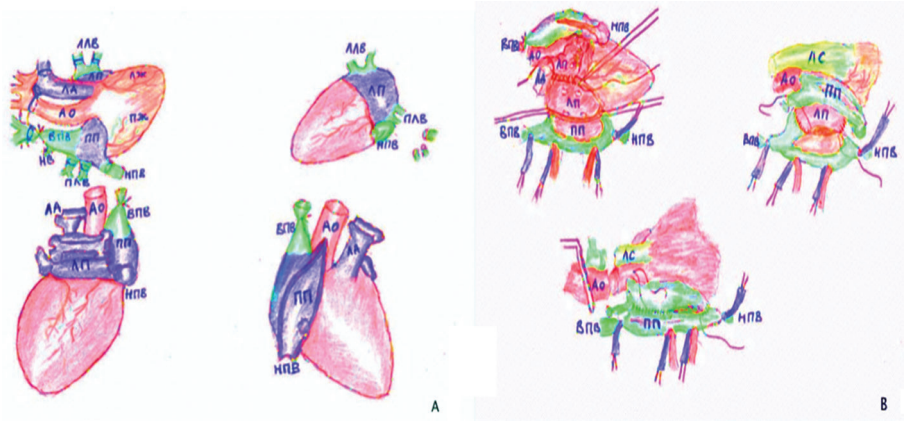

Fig. 2. A - scheme of donor heart removal, B - scheme of donor heart implantation. Abbreviations: Ao - aorta, ЛА - pulmonary artery, ЛП - left atrium, ПП - right atrium, ЛЖ - left ventricle, ПЖ - right ventricle, ВПВ - superior vena cava, НПВ - inferior vena cava, ЛЛВ - left pulmonary veins, ПЛВ - right pulmonary veins.

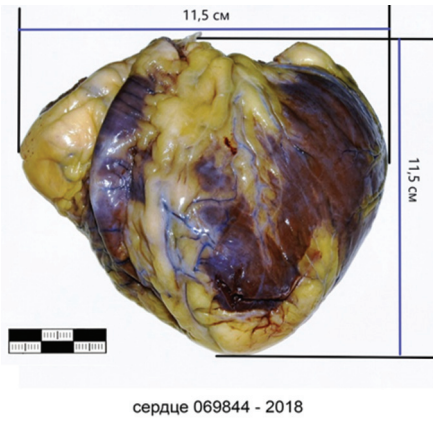

Fig. 3. The heart of the recipient A. 58 years old, without atria. Mass without atria was 385 grams (normal heart mass is 250-280 gr.). Dimensions 11.5x11.5x5.5 cm

ies and SVC. After the final assessment, the removed heart was placed in a three-layer sterile package: the 1st layer with Custodiol, the 2nd with ice water, the 3rd with ice and transported in a special thermal container to RH#1.

After completion of the donor heart collection stage, the surgery was started on the recipient. The operation was performed under artificial blood circulation (IC) and hypothermia up to 28 ° C. The heart of the recipient was explanted, leaving venae cavae with atrial areas and forming a site with the mouths of the pulmonary veins, the ascending aorta and the pulmonary artery (Fig. 3). The OTHT operation was performed using the biatrial technique. Stitching the donor heart to the recipient was started from the left atrium. Due to the flaccidity of the walls of the atrium of the recipient, the anastomosis of the posterior wall between the left atria was performed with a double-row suture (Fig. 2B). In our opinion, such a suture should be applied immediately in order to prevent bleeding, since subsequently it will be technically difficult to carry out hemostasis in this hard-to-reach area. After the anastomosis between the atria anastomoses of the pulmonary artery and then the aorta were formed. The duration of the clamping of the aorta was 2 hours and 8 minutes, the time of artificial blood circulation was 3 hours and 28 minutes, the total surgery time was 5 hours and 15 minutes. Ischemia time of the donor heart was 2 hours and 48 minutes.

Trachea extubation was performed on the first day 8 hours after the OTHT. Cardiotonic support was carried out with moderate doses of adrenaline and dopamine. In the early postoperative period, signs of renal failure were observed with an increase in creatinine up to 330 mmol/l, which was resolved with conservative therapy and a reduction in the dose of tacrolimus.

Immunosuppressive therapy was carried out in a three-component scheme, including a calcineurin inhibitor (tacrolimus), mycophenolate (sodium mycophenolate) and a corticosteroid (metipred). To identify early signs of rejection and graft dysfunction, echoCG and measuring of myocardial necrosis markers were performed daily. An endomyocardial biopsy was also performed on the 5th and 11th day after the operation, also before the patient's discharge on the 26th day, which confirmed the absence of cellular and humoral rejection. Coronary angiography was performed on the 26th day after the HT, which did not reveal hemodynamically significant stenosis (Fig. 4).

The patient was discharged in a satisfactory condition on the 28th day for further postoperative rehabilitation, outpatient treatment and dynamic observation.

Four months after the OTHT at the control examination, the patient feels satisfactory, does not show any special complaints, notes a significant increase in exercise tolerance. According to EchoCG, the systolic function of the left ventricle is preserved (EF = 69%), the left-ventricular diastolic diameter is 4.4 cm. An endomyocardial biopsy was performed, confirming the absence of signs of rejection. Considering the early postoperative period, immunosuppressive therapy was continued according to a three-component scheme: Tacrolimus, Myfortik, Metypred.

Discussion. The first successful heart transplantation in the Far Eastern Federal District showed the possibility of performing this operation in remote regions of the Russian Federation. In this clinical case, the achievement of a positive result was due to the existence of large multidisciplinary medical centers with appropriate material and technical equipment, qualified personnel and highly professional solution of organizational issues on the transplantation of cadaveric organs. Thus, taking into account the socio-

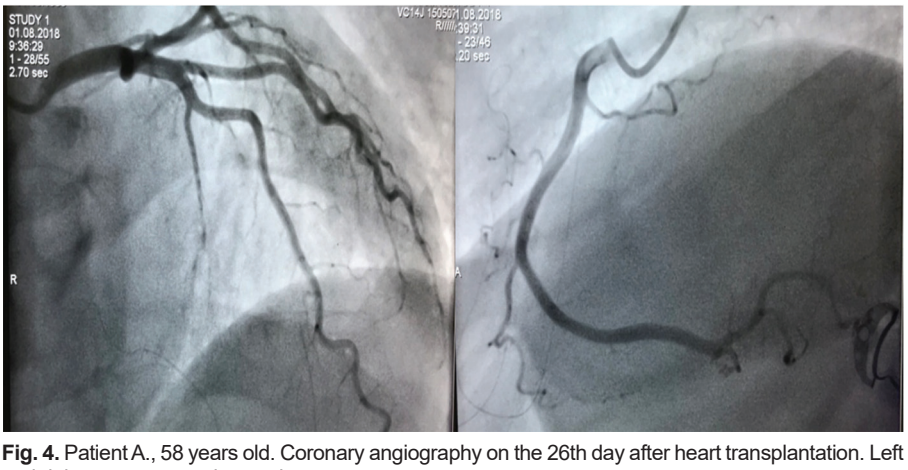

Fig. 4. Patient A., 58 years old. Coronary angiography on the 26th day after heart transplantation. Left and right coronary arteries pool.

economic, climatic and geographical features of the Republic of Sakha (Yakutia), the development of transplantology in the largest region of the Russian Federation is a necessary measure to improve the quality of high-tech medical care in cardiovascular surgery.

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TECHNICAL FEATURES OF THE KIDNEY LAPAROSCOPIC RESECTION WITH SUPER-SELECTIVE BALLOON EMBOLIZATION OF THE RENAL ARTERY

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ABSTRACT

The article is devoted to the study of the results in the surgical treatment of patients with renal neoplasms using a new method of kidney resection, which has its own technical features.

Their essence lies in the temporary superselective embolization of the renal artery, which allows turning off the affected part of the kidney from the circulation. Embolization allows minimizing the blood loss that occurs as well as preserving blood flow in the unaffected areas of the kidney, thereby protecting the remaining part of the kidney from ischemia. As a result, the postoperative period proceeds with a more rapid recovery of kidney function.

Objective: to improve the results of renal neoplasms surgery.

Materials and methods. Laparoscopic resection of the kidney with superselective balloon embolization from October 2015 to October 2017 was performed in 14 patients. The average age of the operated was 54.5 (from 29 to 72) years, among them 3 men and 11 women.

Conclusion. The proposed method of superselective balloon embolization of the renal artery intraorganic branches has it's peculiarities which make it possible to perform a complete intraoperative hemostasis of the renal parenchyma segment in which the tumor-like formation is located. At the same time, the functional state of the rest of the kidney does not decrease, transluminal temporary embolization of the segmental or lobar artery of the kidney reliably blocks the blood flow, preventing massive uncontrolled bleeding. Maintaining blood flow to the intact parenchyma is an important factor in preventing acute kidney damage during organ-sparing operations. No need for skeletonization of the kidney arteries for their temporary clipping allows laparoscopic resection of the kidney to mid-level urological endosurgeon physicians without the help of highly skilled experts, which implies massive use of this technique in multidisciplinary clinics.

Keywords: selective renal artery embolization, kidney resection, kidney neoplasms, minimally invasive kidney surgery.

Introduction. Over the past decade, an increase in the number of patients with kidney cancer has been recorded worldwide. This is undoubtedly due to the wide spread of various methods of early diagnosis, which, in turn, leads to the fact that in 60-70% of patients a localized form of the disease is revealed [1, 5, 8, 10, 15, 23]. In 2014, Schiffmann et al showed that open radical nephrectomy was still the method of choice for stage T1 kidney cancer [19]. However, the initial stages of T1-T2 are increasingly becoming indications for resection of the kidney [6, 8, 9, 12, 17, 18]. Kidney resection is comparable to a total nephrectomy for oncologic outcomes [13]; overall survival of patients [21] is higher and long-term renal and cardiovascular function [11, 22] is better. Thus, according to the principles of the European Association of Urology [7], nephron-sparing surgery is shown for kidney cancer stage T1 [4, 14, 19].

Kidney resection for tumors with a size of less than 4 cm with the improvement of laparoscopic technology is increasingly performed by laparoscopic access [8].

Resection of a malignant tumor of the kidney is only possible while observing the principles of ablastics, for which an adequate hemostasis in the surgical wound is necessary for visual control of the surgical edge. Bleeding can be avoid-

ed, as a rule, by carefully isolating the kidney vessels with an en-block clamping (artery and vein together) or by isolating and shutting off the blood flow in the renal artery or in its segments.

Skeletonization of the renal artery individual segments is a laborious and very complex process, not always feasible due to the anatomical features of the blood supply to the kidney. Clamping of the vascular pedicle or an isolated renal artery to achieve hemostasis threatens ischemic damage to the renal tubules, which are acutely responsive to hypoxic conditions [16, 20].

Currently, a method has been proposed of laparoscopic kidney resection with superselective balloon embolization of the segmental branches of the renal artery during renal parenchyma formations [2]. An assessment was made of the functional state of the operated kidney in the early postoperative period [3].

Objective: to improve the results of renal formations' surgery.

Aims:

1. To evaluate technical features of a kidney tumor laparoscopic resection method with preliminary superselective balloon embolization of the segmental branches of the renal artery.
2. To study the surgical treatment results at patients with kidney tumors after using organ-preserving resection of the kidney.

Materials and methods of the research. Laparoscopic resection of the kidney with superselective balloon embolization from October 2015 to October 2017 was performed in the Urology Department RH No. 1- National Center of Medicine in 14 patients, 3 men and 11 women. The average age of the operated was 54.5 (from 29 to 72) years.

In 6 cases the tumor was located on the right, in 8 - on the left; in 7 cases the lower segment was affected, in 3 - the upper segment, in 4 - the middle segment. The size of the neoplasm ranged from 0.9 to 3.8 cm, averaging 2.2 cm. All patients underwent routine studies in the preoperative period: ultrasound of the urinary system, multispiral computed tomography (MSCT) with contrast enhancement, rentographic examination, separate assessment of renal functions. The degree of difficulty of the proposed kidney resection was assessed according to the R.E.N.A.L scale. on the basis of MSCT data, the average score made up 5.3 points, which corresponds to a mild degree of resectability of the tumor.

Embolization of the segmental renal artery supplying the segment of the kidney with a tumor was performed by the first stage, immediately before the laparoscopic stage of surgical treatment. After performing aortography and determining the localization of the renal artery orifice, a catheter was brought into the renal artery, then a microconductor was installed in the renal artery under the control of fluoroscopy and a coronary balloon 2.5-3.5 mm in diameter was inserted through it. On selective renal angiography, the diameter of the segmental vessel to be embolized was preliminarily measured to select the optimal size of the coronary balloon. Inflating it under pressure up to 20 atmospheres to achieve occlusion and cessation of blood flow in the parenchyma led to reliable hemostasis, which was controlled by performing a control renal angiography. Immediately after reaching a reliable occlusion of the segmental artery, the patient was transferred to the operating room and proceeded to the 2nd stage of surgical treatment. Standard laparoscopic access was performed to the retroperitoneal space by transperitoneal access. After opening the fascia of Gerot, the surface of the kidney with a tumor was isolated from the perirenal fiber. The resection was made with cold scissors, some 3-5 mm from the edge of the tumor. Minor venous bleeding was dried with an electroaspirator. After resection and closure of the kidney wound, the balloon was immediately blown off, causing blood flow to the ischemic area.

Results and discussion. According to the results of a postoperative histological study, 7 patients were diagnosed with a clear cell variant of renal cell carcinoma, in 3 - papillary, in 3 - angiomyolipoma, in 1 - lymphangioma.

Selective renal angiography in an X-ray surgery room is a standard procedure that can be performed by a X-ray surgeon of any qualification (Fig. 1). In carrying out this study, the fact that the presence and participation of the operating surgeon, who will subsequently carry out the operational manual, deserves special attention. Real-time angiography data provide additional and very valuable information about the topography of the kidney, its blood supply, localization of the pathological formation, its vascularization and exact dimensions. The possibility of 3-D visualization of the vessels architectonics gives a clear idea of the nature of the blood supply to the kidney.

Then, with the direct participation of the operating surgeon, a selection is made of the segment of interest of the

Fig. 1. Selective renal angiography. A tumor of the lower segment of the left kidney is determined.

common artery that feeds the segment with formation and is subject to embolization. In this case, the surgeon clearly understands the entire volume of the ischemic parenchyma to prevent uncontrolled bleeding.

The X-ray features of this procedure are to accurately set the embolization balloon in the right place and to ensure reliable arterial hemostasis. To carry out this crucial step, it is more convenient to use arterial catheters with insertion into the lumen of the renal artery, for more precise control over the manipulation of the conductor with balloon. Control angiography with a bloated balloon is required to control the quality of embolization and determine the volume of the ischemic parenchyma (Fig. 2).

The implementation of balloon embolization is preferable to coronary spherical balloons due to the possible complex course of intraorgan vessels not capable of extension. In this case, installation of an elongated cylinder with a length of 2

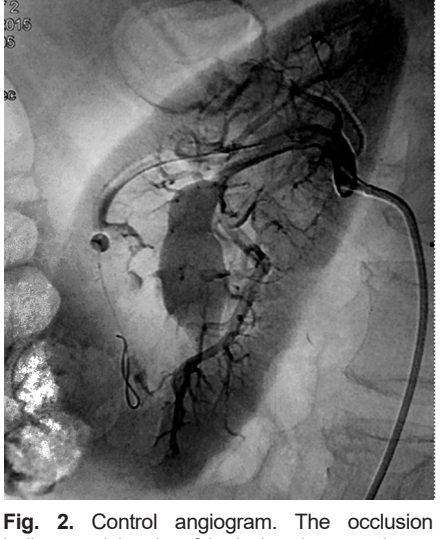

Fig. 2. Control angiogram. The occlusion balloon and the site of the ischemic parenchyma are determined.

cm is difficult.

The laparoscopic stage of this technique has its own characteristics. Access to the operated kidney is possible through any of the standard approaches: transperitoneal, through the abdominal cavity with the imposition of carboxyperitoneum, or at certain locations of the tumor (the back surface of the kidney) - lumboscopic. The latter is less convenient due to the small amount of operational space, but with the appropriate skill and level of skill of the surgeon is quite acceptable.

An important advantage of this technique at this stage is that there is no need to isolate the entire kidney and the vascular pedicle for clamping or temporary clipping of the entire kidney vessels, only the renal artery or lobar arteries to achieve intraoperative hemostasis. In the usual practice of kidney resection, this procedure is technically difficult: the isolation of the kidney vessels requires a high level of operator skill, is fraught with hemorrhagic complications and thereby inevitably lengthens the time of surgery. Skeletization of the lobar arteries is sometimes completely impossible due to the different features of the anatomical structure of the renal vessels. All these difficulties can be avoided when intraoperative hemostasis is performed by the endovascular method. The surgeon can only access the surface of the kidney with the formation, expose a small, but sufficient for a complete resection section of the surface of the kidney with a tumor (Fig.3). In addition to saving time and effort, this approach is considered from the point of view of nephroprotection, as the most benign method of kidney resection. The absence of the need to isolate the entire surface of the kidney undoubtedly has a positive effect on the functional state of the organ as a whole.

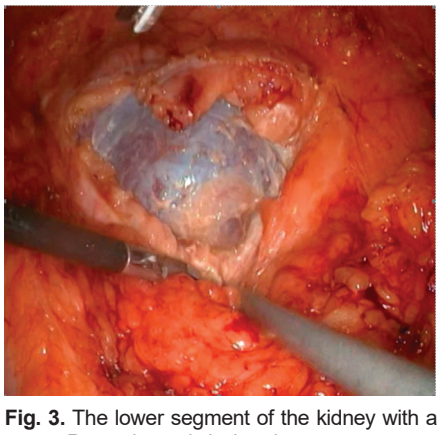

Fig. 3. The lower segment of the kidney with a tumor. Parenchyma is ischemic.

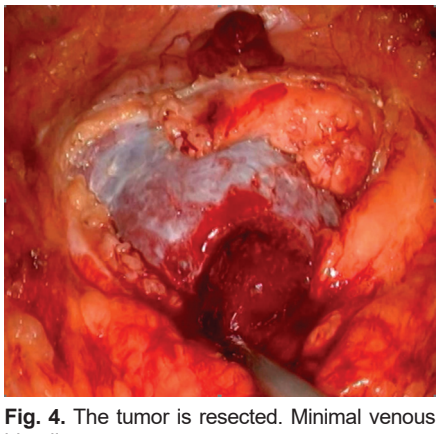

Fig. 4. The tumor is resected. Minimal venous bleeding.

Kidney resection is performed with cold scissors, within the limits of healthy tissue, 3-5 mm from the tumor, which ensures minimal damage to the intact parenchyma (Fig. 4). The absence of arterial bleeding ensures complete control over the dissection plane, which allows you to precisely control the volume of the excised tissue, localize the tumor mass and ensure maximum abdominal resection. Minor venous bleeding is effectively aspirated by a suction pump, which also acts as a retractor for the tissue to be removed. The removed preparation is immediately placed in the endoscap for complete ablasticity of the operation. The wound of the kidney parenchyma is sutured with standard Z-and P-sutures, imposed with the capture of the fibrous capsule. To save time, fixing biodegradable clips can be used at the ends of the ligature, providing, in addition to the effect of fixation, an additional compression moment on the edges of the kidney parenchyma to achieve reliable final hemostasis. When opening the collector system of the kidneys, which occurs with a deep intraparenchymal arrangement of the absence of active bleeding and, consequently, the blood supply to the renal cup-pelvis system, does not create conditions for tamponade of the renal pelvis and violation of urodynamics, thus there is no need for ureteral stenting. The blood flow to the ischemic segment is performed immediately after suturing the kidney parenchyma under endovideo control by bleeding a balloon inflated in the artery (Fig. 5). In the presence of hemorrhage, the surgeon has the opportunity to impose additional hemostatic sutures on the kidney wound and thereby achieve a reliable final hemostasis.

The only, in our opinion, disadvantage of this method lies in the technological separation of 2 stages: X-ray embolization is performed under conditions of X-ray surgery, and laparoscopic resection is performed in the operating room. This

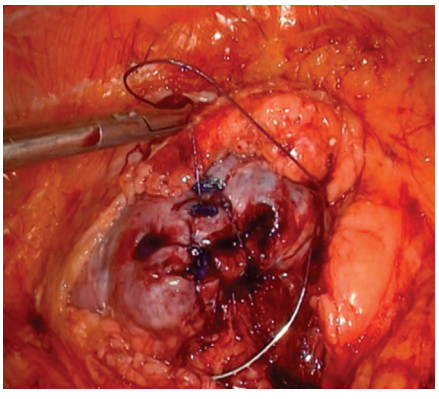

Fig. 5. Starting blood flow. Uniform staining of the parenchyma, the restoration of turgor and the absence of bleeding.

leads to an unjustified lengthening of the thermal ischemia time of the parenchyma area that underwent embolization. This disadvantage can be eliminated by combining both stages in the same room - using a hybrid operating room, equipped with an X-ray surgery unit and a standard endovideo-surgical complex.

Conclusion. The proposed method of superselective balloon embolization of the renal artery intraorganic branches has it's peculiarities which makes it possible to perform a complete intraoperative hemostasis of the renal parenchyma segment in which the tumor-like formation is located. At the same time, the functional state of the rest of the kidney does not decrease, transluminal temporary embolization of the segmental or lobar artery of the kidney reliably blocks the blood flow, preventing massive uncontrolled bleeding. Maintaining blood flow to the intact parenchyma is an important factor in preventing acute kidney damage during organ-sparing operations. No need for skeletonization of the kidney arteries for their temporary clipping allows laparoscopic resection of the kidney to mid-level urological endosurgeon physicians without the help of highly skilled experts, which implies massive use of this technique in multidisciplinary clinics.

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METHOD OF OPTIMIZATION OF TARGETED THERAPY IN PATIENTS WITH GIST GENERALIZED FORM

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ABSTRACT

The purpose of this study: assess the immediate effectiveness, analyze the spectrum of side effects, study the possibilities of optimizing target therapy for patients with generalized forms of GIST based on monitoring the concentration of active metabolites of imatinib mesylate in patients' blood plasma.

Materials and methods: 23 patients with GIST who received targeted imatinib therapy were used to determine the drug's therapeutic concentration level of 1100 ng/ml [link] in the blood plasma by high performance liquid chromatography with tandem mass spectrometry detection (HPLC-MS-MS). All the patients received imatinib therapy in therapeutic regimen with daily intake 400 mg. Within the framework of study before the therapy all the patients underwent the test where the imatinib concentration in blood plasma was estimated using the High-performance liquid chromatography-tandem mass spectrometry method. When the concentration in blood was within the framework of the therapeutic range the revive studies were not carried out. In cases of reduced concentration of imatinib the dose adjustment with subsequent imatinib concentration check was made.

Results and Discussion: Among the patients receiving imatinib in therapeutic regimen with daily intake of 400 mg imatinib active metabolites concentration in blood of 9 (39.1%) patients did not reach the therapeutic level (was less than 1100 ng/ml), in blood of 14 (60.9%) patients was higher than 1100ng/ml (ranging from 1125 to 2584 ng/ml). Imatinib daily intake was escalated to 600 mg for patients whose imatinib concentration in blood at presentation (one month from first imatinib intake) was within the range from 800 to 1099 ng/ml. Daily intake increase to the highest possible recommended amount (800 mg) for 6 (26.1%) patients was determined by the results reflecting at presentation the lowest imatinib concentration in blood – from 0 to 799 ng/ml. Partial effect in terms of size/quantity reduction of metastatic foci was observed among 10 out of 23 (43.5%) patients. Stabilization took place among 9 out of 23 patients (39.1%). Therefore overall efficiency (PE+St) made 82.6% (19/23 patients). Progression was discovered among 4 (17.4%) patients.

Conclusions: In this study for the first time in Russian Federation a possibility of optimization an effective application of imatinib targeted therapy for disseminated forms of GIST was shown. In case of reduced imatinib concentration in blood intake adjustment led to targeted therapy efficacy improvement.

Keywords: gastrointestinal stromal tumor, targeted therapy, imatinib.

Introduction. Practical application of new approaches in diagnosis (based on present knowledge in molecular biology), immune histochemical tests and also the development of targeted therapy have allowed developing an effective algorithm of treating patients with mesenchymal gastrointestinal tumors.

Gastrointestinal stromal tumors (GIST) are the most commonly encountered gastrointestinal sarcomata which were singled out from the group of mesenchymal gastrointestinal tumors for a variety of clinical and morphological features [1, 8, 15, 18].

The degree of GIST incidence is 10-20 cases per population of 1000 000 per year. In the USA 5000-6000 new cases of such diseases are registered every year. GIST morbidity is equal in different geographical regions and among different ethnical groups [4]. Most of GIST develops at the age of 50-70. At any age GIST morbidity is equal among male and female [14].

Experience of application systemic chemotherapy for curing this group of tumors displayed poor result. Neither most commonly used combination MAID nor Dacarbazine and Doxorubicine monochemotherapy were effective: according to different authors the level of response was from 0 to 27% and median overall survival reached only 14-18 months [6].

According to the literature review 80% of stromal tumors have KIT mutations (exons 9, 11, 13, 17), 3-18% - PDGFRA mutations (exons 12, 14, 18) and in 12-15% of the cases of GIST KIT and PDGFRA mutations are absent (wild type genes WT) [3,5,7,14].

Imatinib has been successfully used in curing GIST since 2001 as it is a medicament of neoadjuvant and adjuvant therapy and it is a first line drug for unresectable and/or metastatic GIST.

In some cases the effectiveness of treating patients with GIST is decreasing due to the current problem of progressing drug resistance. Although only 15% of patients with GIST have intrinsic imatinib resistance and its intolerance [11], the disease of the majority of patients who initially had response to the targeted therapy is advancing as a result of acquired resistance [13]. However, in a number of cases the reason of GIST advancing is not an acquired resistance but factors that prevent long-lasting and continuous imatinib intake such as noncompliance of drug therapy, pseudoprogression and other reasons (for example, gastrectomy) [17, 19]. Consequently, before moving to the second-line therapy it is reasonable to pay special attention to the factors of GIST advancing and to exclude other reasons of resistance to imatinib.

It has been demonstrated that median time to progression and overall response rate among GIST patients with active metabolites concentration less than 1100 ng/ml is statistically lower than among patients with higher rate of metabolite concentration[12].

In the majority of cases non-response and progression are attributed to the decrease of imatinib therapeutic concentration in blood plasma which can be caused either by noncompliance of drug therapy [9, 16] or by imatinib metabolism peculiarities of every individual and also by co-medication intake that effects imatinib metabolism [19, 20, 21]. Therefore monitoring of imatinib concentration in blood plasma allows the doctor to exclude possible reasons of observable changes and minimize the risks of drug self-tapering and deterioration of therapy tolerability before it is too late.

The research objective was efficacy evaluation, adverse effects spectrum analysis, investigation of possibilities for optimization of targeted therapy of patients with generalized form of GIST based on the monitoring of imatinib mesylate active metabolites concentration in patients' blood plasma.

Materials and methods. In this research we have analyzed the efficacy and attempt to individualize the treatment of 23 patients with disseminated form of GIST who were receiving medical treatment in several medical institutions: clinical site of the Oncology and Thoracic surgery Department in MONIKI n.a. M.F.

Vladimirskiy and Moscow Oncology Centre №2. All the patients had undergone previous surgical treatment. As part of complete physical examination before including the patients whose disease had progressed into this research study they went through the following tests: chest X-ray, ultrasound investigation and/or abdominal CT/MRT, esophagogastroduodenoscopy, electrocardiography and also morphological examination of postoperative material (histological processing and IHC test).

On clinical site of Central Research Laboratory of Rostov State Medical University we have conducted the estimation of imatinib concentration of therapeutic level 1100 ng/ml in blood plasma of the GIST patients who received imatinib targeted therapy. During this estimation the High-performance liquid chromatography-tandem mass spectrometry method was used.

The evaluation of treatment efficacy was conducted on the basis of dynamic changes observed after the check EGDS. Abdominal ultrasound investigation/CT/MRT were done after 3, 6, 9 and 12 months. In support of primary efficacy parameter analysis the percentage of patients with new metastatic foci was estimated. For evaluation of chemotherapy efficacy we used well known World Health Organization criteria: complete remission (complete regression) - no evidence of tumor; partial remission (decrease of tumor by more than 50%), stabilization (decrease of tumor by less than 50% or increase by no more than 25%), progression (increase of tumor by more than 25% or appearance of new foci) [19].

The evaluation of adverse effects spectrum was conducted based on patients' complaints and medical data which includes laboratory data.

The findings of the study were processed by methods of descriptive statistics. All the calculations were made with the help of analytics software packages «Statistica for Windows. Release 10.0» (STATSOFT Inc.) and SAS.

Before entering the research all the participants signed informed consent to participate in the study. The study was approved by local ethics committee of Yaroslavl State Medical University Ministry of Health of the Russian Federation.

23 patients with disseminated forms of GIST who received imatinib therapy in therapeutic regimen with daily intake 400 mg were included in this study.

The proportion of men and women was 15/8. The average age at the moment of the research was 63,1 years (age range 35,3-78,4years).

By site of primary tumor there was the following distribution: 11 patients (47,8%) had tumor in the abdomen, 7 patients (30,4%) - in small bowel and 5 patients (21,8%) - in large bowel.

The scope of prior surgery depended on the size, the site of tumor and the degree of local spread of the process (Fig.1).

As demonstrated in Fig. 1 the majority of patients (87,0%) underwent conservative surgeries.

Based on the pathomorphological research findings two histological types of GIST were observed: spindle-sell - 82,6% (19 patients) and epitheliocellular - 17,4% (4 patients).

All the patients included in the study underwent immunohistological analysis.

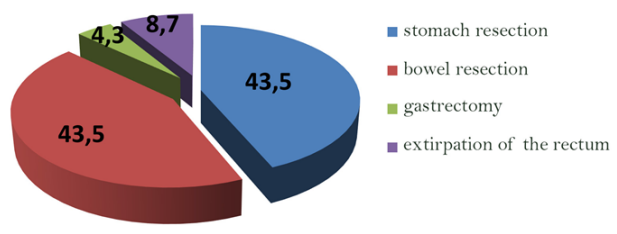

Fig.1. The scope (%) of prior surgery on patients with generalized forms of GIST

For immunohistological analysis a panel of markers including CD117, CD34, vimentin, SMA, desmin, protein S-100 and Ki67 was used. The degree of expression of immunohistological markers was rated on the scale from one to three depending on the intensity of immunohistochemical stains. GIST was diagnosed when there was a tumor cells expression of immunohistochemical marker CD117 (C-KIT). In case of doubtful reaction the presence of CD34 marker and its degree of the expression were taken into consideration. According to the carried out immunohistological analysis gene c-kit expression has been observed in 100% of the tumors. Another marker that allows to differentiate GIST, CD-34, has been observed in 78,3% of the cases which corresponds to the current data reflected in specialized literature [5].

12 (52,2%) patients with disseminated forms of GIST underwent genetic mutation analysis. In 11 (91,7%) cases c-kit gene mutation was identified and in 1 case (8,3%) PDGFRA gene mutation was identified. C-kit exon 11 mutations were identified in 8 (72,7%) cases and C-kit exon 9 mutations - in 3 (27,3%) tumors. The only PDGFRA gene mutation settled in exon 18.

The distribution of metastatic foci depending on the localization was the following: in most cases metastasis settled in liver: solitary lesion of liver was in

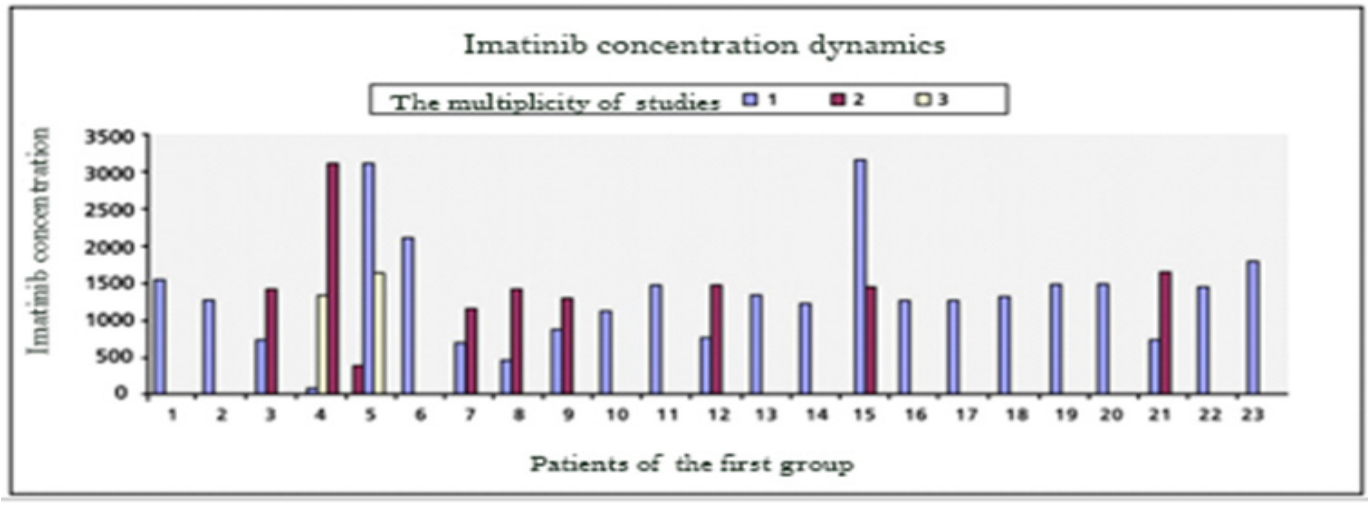

Fig. 2. Imatinib concentration in blood plasma of patients with disseminated forms of GIST

52,2% (12 patients), coexistent with peritoneum affection - in 17,4% (4 patients). Secondary peritoneum changes were observed in 26,1% (6 patients). Metastatic foci in retroperitoneal lymph nodes were identified in 4,3% (1 patient).

All the patients received imatinib therapy in therapeutic regimen with daily intake 400 mg. Within the framework of study before the therapy all the patients underwent the test where the imatinib concentration in blood plasma was estimated using the High-performance liquid chromatography-tandem mass spectrometry method. At the drug concentration in the blood corresponding to the framework of the therapeutic range, repeated studies were not conducted. In cases of reduced concentration of imatinib dose adjustment with subsequent imatinib concentration check was made.

In Fig. 2 the total amount of carried out researches on imatinib concentration in GIST patients' blood plasma and also frequency of examining imatinib detection and concentration in blood of all the 23 patients of this group are reflected.

Results and Discussion. Among the patients receiving imatinib in therapeutic regimen with daily intake 400 mg imatinib active metabolites concentration in blood of 9 (39,1%) patients did not reach the therapeutic level (was less than 1100 ng/ml), in blood of 14 (60,9%) patients was higher than 1100ng/ml (ranging from 1125 to 2584 ng/ml).

The range of imatinib active metabolites concentration discovered during the study is reflected in Fig. 3.

The decision of individualizing the therapy was made according to the results of primary study of imatinib concentration in blood. Imatinib daily intake was escalated to 600 mg for patients whose imatinib concentration in blood at presentation (one month from first imatinib intake) was within the range from 800 to 1099 ng/ml.

Daily intake increase to the highest possible recommended amount (800 mg) for 6 (26,1%) patients was determined by the results reflecting at presentation the lowest imatinib concentration in blood – from 0 to 799 ng/ml.

A month after individualizing the therapy patient subgroup with lowest imatinib concentration at presentation had a follow-up test of imatinib concentration in blood. The following results were obtained: 5 (55,6%) patients had the level of imatinib concentration higher than 1100 ng/ml, concentration of 4 (44,4%) patients continued to be lower than the therapeutic level. During the analysis and possible causes of imatinib concentration decrease identification it was discovered that 2 out of 4 patients had c-kit exon 9 mutation while other two patients independently reduced their daily intake to 400 mg due to the pharmacoeconomic difficulty of community-based drug reimbursement. After cause of imatinib concentration decrease identification patients' daily intake was increased.

The data concerning imatinib therapy success rate are presented in Table №1.

As it appears from Table 1 partial effect in terms of size/quantity reduction of metastatic foci was observed among 10 out of 23 (43,5%) patients. Stabilization took place among 9 out of 23 patients (39,1%). Therefore overall efficiency (PE+St) made 82,6% (19/23 patients). Progression was discovered among 4 (17,4%) patients.

Based on the results of medical checkup 2 patients receiving imatinib daily intake of 400 mg were recorded to have disease progression in terms of expansion in the number of metastatic foci in liver despite achieving the therapeutic level of imatinib concentration in blood plasma. To increase efficiency and achieve objective response to therapy it was decided to increase imatinib daily intake to 800 mg for those patients. Follow-up checkups and monitoring of imatinib active metabolites concentration in blood were conducted after 1, 3 and 6 months. At the end of first month from the start of drug therapy method optimization it was recorded that these patients had trough plasma concentration increased from 200 ng/ml to 1980 ng/ml and from 420 ng/ml to 2458 ng/ml. Control study of abdominal organs (CT/MRT) showed disease stabilization among those patients: quantity, size and spissitude of metastatic foci remained constant after 3, 6 months and follow-up tests.

Adverse effects. Adverse experience connected with imatinib daily intake escalation was observed in 4 cases which made 17,4% of all the patients. 3 patients (13,04%) whose daily intake had been escalated to the highest possible recommended amount (800 mg) complained of temporary swelling and asthenia which did not require drug therapy correction. Moreover, these adverse effects did not require imatinib daily intake reduction due to their not-critical intensity.

Efficacy of imatinib targeted therapy for patients with disseminated forms of GIST

Therapy efficacy	Number of patients	
	Absolute value	Relative value, %
Partial effect (PE)	10	43,5
Stabilization (St)	9	39,1
Progression (Pr)	4	17,4
Overall	23	100

Discussion. In this study we present preliminary evidence of personalised therapy efficacy evaluation among patients with disseminated forms of GIST who have been receiving imatinib treatment.

For the first time in Russian Federation test on imatinib concentration in blood plasma by High-performance liquid chromatography-tandem mass spectrometry method was carried out among GIST patients who received imatinib targeted therapy. We have not found any data using this method with solid tumors in available professional literature. At the present day an attempt to reasonably adjust imatinib daily intake on the basis of its concentration in blood was made for the first time. In case of reduced concentration (lower than the therapeutic level of 1100 ng/ml) intake adjustment was made by titering. Due to the use of this method partial effect in terms of size/quantity reduction of metastatic foci was achieved among 10 out of 23 (43,5%) patients. Stabilization took place among 9 out of 23 patients (39,1%). Therefore overall efficiency (PE+St) made 82,6% (19/23 patients). Drug tolerance was acceptable. Such approach can be a first step in personalized GIST therapy development.

Conclusions. In this study for the first time in Russian Federation a possibility of optimization an effective application of imatinib targeted therapy for disseminated forms of GIST was shown. In case of reduced imatinib concentration in blood intake adjustment led to targeted therapy efficacy improvement.

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THE IMPLEMENTATION OF LIQUID-BASED CYTOLOGY TO IMPROVE DIAGNOSTICS OF CERVIX UTERUS DISEASES

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ABSTRACT
A comparison of cytological results obtained by the method of liquid-based (LBC), implemented in practice on the basis of the laboratory of pathology, histology and cytology of the Clinic of MI M.K. Ammosov NEFU, and the traditional method is done.
It has been confirmed that the diagnostic value of the liquid-based cytology method in the diagnosis of cervical pathology is generally higher compared with TM. It is recommended to supplement the cytological study with a molecular method for the detection of human papillomavirus (HPV testing), which will improve diagnosis and subsequent treatment.
Keywords: cervical cancer, diagnostics, liquid-based cytology, screening.

Relevance. Cervical cancer (CC) is one of the few nosological forms of malignant tumors that meet all the requirements for population-based screening. The disease is widespread and important health issue which has a reliably recognizable preclinical phase and a long period of development. It is possible for further verification of the diagnosis and effective treatment methods, and there is a reliable screening test - cytological examination of smears taken from the cervix and cervical canal [4].

The one of the principal methods in the early detection of precancerous and tumor processes of the cervix is cytological method. It makes to evaluate of epithelium state, to check the presence or absence of cellular response to various effects, and to identify the inflammatory process and some infectious agents [3]. The essential factor in effective cervical cancer screening is the sensitivity of cytological screening. According to various researchers, it ranges from 66% to 83%. The cause of false-negative cytological responses in 70-90% of cases is poor material sampling for cytological examination, and only in 10-30% of cases is a misinterpretation of cytological data [6]. The most commonly nondiagnostic material is obtained in smears from the cervical canal. The absence of endocervical epithelium cells in smears is noted in 8-18% of cases. As a result, it is glandular and adenosquamous CC that is most often missed during the screening [4].

It is necessary to use modern methods and to implement new clarifying diagnostic for maximum optimization of cervical pathology diagnosis and the avoidance of subjective intraoperative measurement of the location and size of plot neoplasia. Today, highly effective method of liquid cytology (LBC) are gaining ground, which give a thin representative monolayer drug with a minimum content of blood, bacteria and neutrophilic leukocytes. Wet fixation enhances the clarity of structures, common artifacts are absent. The sensitivity of the cytological method in the application of LBC increases to 85% [1]. Also, the LBC peculiarity is in fact, that one material sampling is able to give 6 «serial» (the same cell composition) smears. It makes possible to use additional research methods, for example, HPV testing, immunocytochemical determination of tumor markers [2]. Taking it into account, the liquid technology of cervical samples production was introduced into clinical practice on the basis of the Laboratory of Pathomorphology, Histology and Cytology of the Medical Institute Clinic of NEFU, Yakutsk from August 2018. However, LBC is highly specific and should be supplemented by molecular diagnostic methods. Detection of human papillomavirus DNA has more sensitivity to the diagnosis of precancerous and CC than to cytology, which is then able to detect early precancerous changes of the cervix, therefore, reduces the risk of developing CC [5, 7].

The purpose of the study is to use the embedded method of liquid-based cytology to conduct a comparative analysis of the results of cytological examination of material from the cervix obtained by the traditional method and the method of liquid-based cytology.

Materials and methods. In the clinical laboratory of pathomorphology, histology, and cytology on the basis of M.K. Ammosov NEFU Medical Institute, 35 screening of cervical samples was conducted in the parallel with traditional method and liquid-based cytology with the preparation of a cytological drug on the automated system CellPrep Plus (Korea). The material was taken from the patients after examination and extended colposcopy in the «Malex+» clinic. The age of the patients ranged from 23 to 54 years. The diagnosis was conducted by Romanovskiy - Gimza stain method. Special attention in the screening was paid to the completeness of obtained material (the adequacy of the smear). Diagnostic accuracy of cytological material screening of the cervix depends largely on the quality of the material. If smears have cells of endocervical, flat and metaplastic epithelium, the material is adequate for the study. It is very important to take into account that such material should be obtained from the transformation zone – the area- where the tumor most often occurs. If the material is represented by a very small number of cells, a large number of blood elements, mucus, and the presence of artifacts, which makes impossible to properly assess the cytological picture, it is considered inadequate. Cytological diagnosis was made in accordance with the clinicopathologic classification of J. V. Bokhman (1976), and with the commonly accepted criteria for assessing the state of the epithelium by Bethesda System (1999). Detection, typing (co-testing) of human papilloma virus (HPV) (6, 11, 16, 18, 26, 31, 33, 35, 39, 44, 45, 51- 53, 56, 58, 59, 66, 68, 73, 82 serotypes) by PCR was performed on the basis of microbiological laboratory of the Medical Institute clinic based on NEFU.

The results and discussion. The percentage of background detection and precancerous pathology was estimated when comparing the traditional cytological study with the method of liquid-based cytology. It found a small difference between traditional smears and smears obtained by the LBC (Fig.1). The absence of intracellular lesions (cytogram without features) was revealed by traditional cytology in 10 (28.5%) patients, by LBC (NILM) in 23 (65.7%) patients, among them 9 (25.7%) patients with no pathology and 14 (40%) patients with reactive changes (squamous metaplasia, inflammation, moderate hyperplasia). Cervical pathology was revealed during the routine cytological examination in 71.4% of cases, and during liquid cytology in 74.3% of cases. Reactive changes in TM were 13 (37.1%) cases when in LBC were 14 cases, 40% of the total number of women studied.

The mild cervical dysplasia was established by the traditional method in 10 (28.5%) cases, in 2 (5.7%) cases of which have indirect signs of viral infection. Liquid-based cytology LSIL revealed in 11 cases (31.4 percent), of which CIN I in 7 (20%) cases, CIN I with koilocyte in 3 (8,6%) cases, and the presence of koilocytes with reactive changes in 1 case (2.8%) (Fig.2 (a, b)).

In 2 women (5.7%) revealed moderate dysplasia by TM, and in 1 case (2.8%) of the total number of women surveyed was recognized by LBC HSIL.

The use of co-testing confirmed HPV carriage in 3 women diagnosed by LSIL, of which 1 woman confirmed the presence of HPV 16,39 types; 1 woman was diagnosed with HPV 6 type; 1 woman HPV 68,39 types. 1 woman was diagnosed HPV 16 and 51 types by NILM. 3

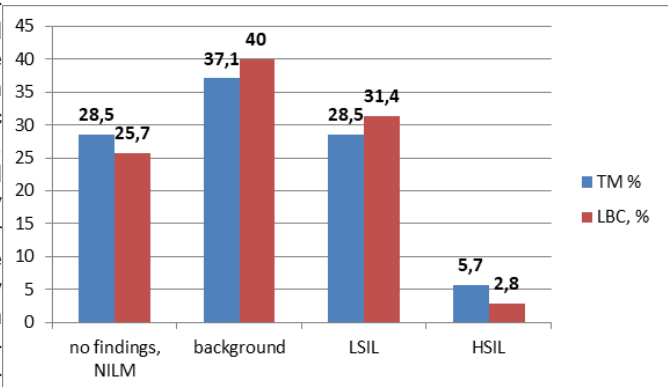

Fig.1. Comparative characteristics of cervix uterus disease diagnosis by the traditional method and the liquid-based cytology.

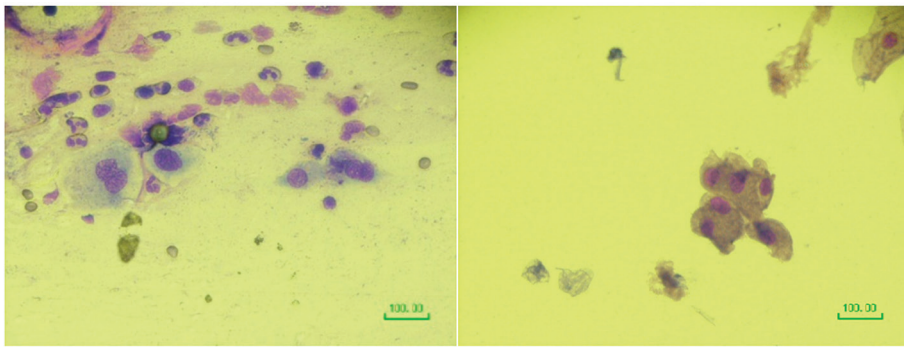

Fig.2. Binuclear or «kissing» nuclei in cervix smear for papillomavirus infection (conventional smear) (a) and koilocyte for liquid-based cytology (staining method by Romanovsky-Gimza), x400 (b)

negative cases were identified in the diagnosis by LSIL, which indicates the beginning of a viral lesion or other causes of dysplasia.

Thus, the diagnostic value of liquid-based cytology method in the diagnosis of cervical pathology is generally higher compared to the traditional method. The LBC method is more informative and can be used as an independent screening method for detecting cervical disease. Liquid-based cytology method in cervical cancer screening supplemented by a molecular method of virus detection (HPV testing) will enable to reveal the initial, precancerous stages and specific treatment in time.

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OPTIMIZATION OF AUTOPLASMA DONATION DURING PREGNANCY

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ABSTRACT

The article reflects the experience of autoplasma donation in pregnant women with threat of massive bleeding in the period from 2016 to 2018. Analysis of the statistics of massive bleeding according to the diagnosis is presented. According to the analysis, pathologies of pregnancy, related with the greatest risk of massive bleeding were identified. We also optimized the management of autoplasma donation in these groups of pregnant women.

Keywords: autoplasma donation, massive bleeding, obstetrics.

Introduction. Massive bleeding with the loss of more than 30% of the blood volume remains one of the most frequent causes of maternal mortality around the world [1. 6, 7].

When massive bleeding occurs, one of the main part of the treatment is transfusion therapy, which is accompanied by number of immune and non-immune complications [4].

Due to blood-saving technologies it is possible to avoid reactions and complications during transfusion therapy in massive bleeding. One of the methods is donation of autoplasma, which consists of preparing patient's own plasma with further autologous transfusion. The advantages of autoplasma transfusion are: no risk of post-transfusion reactions, complications, blood-transmissible infections, no danger of alloimmunization [2, 5].

Optimization of autoplasma donation in pregnancy is a significant part of successful treatment of massive bleeding in obstetrics.

Objective of research: optimization of autoplasma donation in pregnancy. Reducing the number of reactions and complications during transfusion therapy in the treatment of massive hemorrhage in obstetrics.

Materials and methods of research. During the period from 2016-2018 in "Perinatal center" of Khabarovskii krai autoplasma preparation was made among 216 patients with various diagnoses. 2016 - 119 patients, 2017 - 63 patients, 2018 (10 months) - 34 patients. Detailed list is presented in Table.

Preparation of autoplasma was made in the period of 32-37 weeks of pregnancy in patients threatened by massive bleeding (the list of patients threatened by massive bleeding is presented in the Guidelines "Prevention, treatment and algorithm of management in obstetric bleeding" [6]). The preparation of autoplasma was performed by the method of plasmapheresis in the department of extracorporeal hemocorrection methods. One donation was about 400 - 600 ml, depending on the patient's weight and the tolerance of the procedure itself (hemodynamic reactions to blood sampling).

Tests complex before the procedure included: testing for HIV-1 / HIV-2, RW, hepatitis B and C; hemostasiogram; blood group, Rh factor; clinical blood test; total blood protein, ALT, AST.

Also all the patients filled a form about their attitude to autoplasma donation and autoreinfusion of red blood cells.

After the plasmapheresis, all patients underwent the replacement of the lost plasma volume with crystalloid solutions in a 1: 1.5 ratio.

Results and discussion. The analysis of the obtained data revealed that 15 out of 216 patients who donated autoplasma, occurred massive blood loss during C-section, pathological blood loss (more than 1000 ml, but less than 30% of the circulating blood volume) - in 18. It should be noted, that all patients underwent a cesarean section; no significant blood loss was observed during independent delivery.

Analyzing the diagnoses of patients with massive blood loss, it was noted that all cases fit into two diagnoses: placenta increta - 11 (2016 - 3, 2017 - 4, 2018 - 4) and the full variant of placenta previa - 4 (2016 - 2, 2017 - 0, 2018 - 2). In patients with pathological blood loss, only one diagnosis was observed: the full variant of placenta previa - 18 (2016 - 7, 2017 - 6, 2018 - 5).

It was also revealed that the average level of fibrinogen in patients who underwent autoplasma donation was 3.23 g / l (2.7 - 5.6).

Out of the 216 cases, autoplasma was utilized in 39% of cases (Lack of demand) (2016 - 26, 2017 - 12, 2018 - 1).

Conclusion. According to the analysis of the results, we were able to draw the following conclusions:

1. According to the European guidelines for the management of massive hemorrhage [8], an effective starting dose of the freshly frozen plasma in the treatment of massive blood loss is 10-15 ml / kg of body weight. But this dose should be doubled if coagulopathy was developed. Thus, autoplasma donation in pregnant women of high risk should be done in doses of 10-15 ml / kg. However in the case of patients whose risk of massive hemorrhage is definitely 100% (i.e placenta increta), we consider appropriate to double the autoplasma donation dose in the absence of contraindications.
2. The average level of fibrinogen in autoplasma donors was 3.23. Due to the fact that this test is not routinely held at blood transfusion departments, it is impossible to say in which cases the level of fibrinogen in donors' fresh frozen plasma reaches the normal level, and, in particular, the level observed among women in the third trimester of pregnancy. This fact indicates the high efficiency of autoplasma, thus the average level of fibrinogen in pregnant women' autoplasma is clearly higher than the average normal rates and never approaches the lower limit of normal.
3. According to our data, massive

Frequency of donation and utilization of autoplasma due to lack of demand, depending on the diagnosis, n (%)

Diagnosis	2016		2017		2018	
	Prepared	Utilized	Prepared	Utilized	Prepared	Utilized
Placenta increta	3	0	3	0	4	0
Full variant of placenta previa	13 (100)	2 (15,4)	17 (100)	1 (5,88)	17	0
Marginal variant of placenta previa	18 (100)	5 (27,7)	3 (100)	2 (66,6)	4	0
Triplets	1	0	0	0	1	0
Twins	6 (100)	1 (16,6)	3 (100)	1 (33,3)	1	0
Insolvent scar after 1 C-section	22 (100)	3 (13,6)	14 (100)	2 (14,3)	0	0
Insolvent scar after 2 C-sections	34 (100)	5 (14,7)	13 (100)	2 (15,3)	3	0
Insolvent scar after 3 C-sections	8 (100)	2 (25)	6 (100)	2 (33,3)	2	0
Insolvent scar after 4 C-sections	2 (100)	2 (100)	0	0	0	0
Uterine myoma	7 (100)	3 (42,8)	0	0	1	0
Hypotonic bleeding in anamnesis	0	0	1	0	0	0
Big fetus	0	0	2 (100)	1 (50)	0	0
Menier disease	0	0	1 (100)	1 (100)	0	0
Pregnancy induced arterial hypertension. Osteochondrosis of lumbar area	1	0	0	0	0	0
Compound ob-gyn anamnesis	2 (100)	2 (100)	0	0	0	0
Suspicion of placenta previa	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Overall	119 (100)	26 (21,84)	63 (100)	12 (19)	34 (100)	1 (2,94)

bleeding was observed only in patients with placenta increta (100% cases) and full variant of placenta previa (8.3% of cases), pathological blood loss was observed only in patients with full placenta previa (37.5%). In other cases, blood loss was insignificant and did not require autoplasma replacement transfusion, as a result of which the plasma had to be utilized.

Based on the above, we believe that the donation of autoplasma is appropriate in patients with diagnoses such as: placenta increta and the full variant of the placenta previa. According to previously calculated statistics in the Perinatal Center of Khabarovsk, among 27 patients who underwent surgeries from 2016 to 2018 (6 months), with placenta increta, massive bleeding was observed in 100% of cases [3]. This fact confirms that autoplasma donation is a necessary part for preparation before the cesarean section. In other cases, autoplasma donation is impractical.

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RATIONAL METHODS OF DIAGNOSTICS OF CHRONIC ENDOMETRITIS TYPES AFTER PREGNANCY TERMINATION AMONG WOMEN WITH CHRONIC PYELONEPHRITIS AND ANEMIA

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ABSTRACT

The article shows different effectiveness of endometrial evaluation methods among women with pregnancy termination on the background of CP and anemia, their complementarity in the allocation of CE types – a proven cause of early reproductive losses. Clear connection is obvious between the lack of pregravid preparation on the background of chronic EGD and high CE frequency, the diagnosis and the treatment of which at the pre-grading stage seem to be the best tactics for the prevention of various degrees of violations of the “fetal-endometrial” interaction.

Objective of the research: to evaluate the effectiveness of the diagnostic stage in the management of women after abortion on the background of chronic pyelonephritis (CP) and anemia.

Materials and methods of the research: A group of 431 women with terminated pregnancy due to anemia (n=246) and CP (n=185) was prospectively examined.

Research methods: clinical and statistical analysis, sonography, hysteroscopy, pathomorphological examination of the biopsy of the uterine mucosa/removed material with visually obvious pathology and/or revealed by sonography.

Results of the research: The effectiveness of diagnosing chronic endometritis types (hypoplastic and hyperplastic) with hysteroscopy is shown and confirmed morphologically – with the allocation of characteristic features, typical of each group.

Indicators of sensitivity and specificity of methods for diagnosing the hyperplastic type (92.6% and 66.7% - sonography, 97.5% and 77.2% - hysteroscopy) were higher than with the hypoplastic one (79.2% and 68.6% - sonography, 89.6% and 74.4% -hysteroscopy). The histological verification of the CE (chronic endometritis) pattern took place in 83.5%, with a greater frequency of the hypoplastic variant in CP (50.3% versus 24.8% in anemia) ($p < 0.05$) and hyperplastic - in half of the samples with anemia - one and a half times more often ($p < 0.05$). The amount of samples with an “incomplete” CE morphological picture in the EGD (extragenital diseases) group was 39.2%.

Detailing of endometrial histological studies in a group of women with pregnancy termination on the EGD background showed the presence of

endometrial polyps - in 5.5%, intrauterine synechium - 2.0%, unchanged mucosa - 9.3%.

Different effectiveness of endometrial evaluation methods among women with pregnancy termination on the background of CP and anemia shows their complementarity in the allocation of CE types – a proven cause of early reproductive losses. Clear connection is obvious between the lack of pregravid preparation on the background of chronic EGD and high CE frequency, the diagnosis and the treatment of which at the pre-grading stage seem to be the best tactics for the prevention of various degrees of violations of the "fetal-endometrial" interaction.

Conclusion:

Clarification of the concepts of CE pathogenesis in hypo- and hyperplastic types during a comprehensive study of women with abortion on the EGD background will allow for differentiated management tactics, involving a set of measures to restore the structural and functional viability of the uterine mucosa.

Keywords: hypoplastic and hyperplastic types of chronic endometritis, hysteroscopy, endometrial pathomorphology, extragenital diseases.

Introduction. Seeing chronic inflammation of the uterus as the leading cause of non-developing pregnancy is a fact, fully recognized by the world community, but in practice we have a big number of unrecognized diseases, mostly of low-intensity character on the background of dominant abortive Russian "mentality" and the lack of rehabilitation procedures for the injured by surgical manipulations inflamed endometrium. [4]. Predictors of endometrial inflammation are thought to show a tendency of adherence to aggressive tactics of uterus curettage instead of medical evacuation during non-developing pregnancy and less traumatic aspiration emptying in cases of abortion / miscarriage [2,8].

The statement of the high frequency of infectious and inflammatory diseases, obstetric and perinatal complications among pregnant women with anemia and chronic pyelonephritis (CP) does not exclude the possibility of exacerbation of the inflammatory process in the uterus [10]. The background predisposing to reproductive losses, according to some authors, is an imbalance between the hormonal and immune systems of the body and pathogens – representatives of the genital tract loci biocenosis [1].

Echographic screening for CE detection is considered to be uninformative, but it is believed to be necessary to focus on the individual features that contribute to its diagnosing [7]. The non-invasive assessment of the endometrium is complemented by dopplerometry of the organ vessels, allowing to estimate trophic reserves, to identify the relationship of hemodynamic and the degree of degenerative changes [5].

The recognition of hysteroscopy as an effective method of diagnosis is undeniable, especially with the appearance of works on the possibilities of CE types gradation on the basis of individual hysteroscopic stigmas [10, 13]. According to the data, it is the visual CE signs that make it possible to verify variants of the disease, the diagnosing difficulty of which is associated with local and erased forms. Suggestions to consider a change in the colour of the endometrium and its thickness as markers of chronic endometrial inflammation are thought by some researchers to be sufficient for identification, while others report only a third of cases in the existing disease [11, 12].

Opinions on the specificity of echography and hysteroscopy in CE detection are ambiguous, in particular, due to the comparable frequency of individual signs of the disease in various pathomorphological forms [9, 13]. The most objective method of diagnosing the disease is the pathomorphological study of the endometrium, with clearer criteria in contrast to the insufficiently specific echographic and sonographic markers [12]. Overcoming of low detection rate of the disease is achieved by unification of the criteria for non-invasive diagnostic methods in terms of variants of uterus chronic inflammation. The complexity of CE morphological interpretation is determined by histobiological characteristics, typical of different phases of the menstrual cycle, which indicate the necessity for conducting research in the early proliferative phase. Varying degrees of lymphocytic infiltration and stroma fibrosis also present an incomplete morphological picture in the chronic inflammatory process in the uterus showing one of the signs – inflammatory infiltrates or lymphoid follicles [12].

Discussions continue on the validity of CE detection, taking into account dystrophic changes in the mucosa and factors predisposing to their development, along with allegations of compliance of clinical and morphological forms of inflammation to their morphological manifestations [3]. It seems that the clarification of the pathomorphosis of CE forms, reflecting different pathogenesis of the disease, will allow for a differentiated choice of treatment tactics for women with reproductive failures and chronic EGD (extragenital diseases).

Objective of the research: to evaluate the effectiveness of the diagnostic stage in the management of women after abortion on the background of CP and anemia.

Materials and methods of the research: A group of 431 women with terminated pregnancy due to anemia (n=246) and CP (n=185) was prospectively examined in the first trimester of pregnancy. Written informed consent to participate in the study was obtained from all patients.

Criteria for inclusion in the study: the presence of a history of reproductive losses (up to two months after pregnancy termination).

Research methods: clinical and statistical analysis, sonography, hysteroscopy, pathomorphological examination of the biopsy of the uterine mucosa/removed material with visually obvious pathology and/or revealed by sonography.

Mathematical processing of the data was performed with standard software packages for Windows version 20 (SPSS Inc., Chicago, IL).

Statistical processing of the studied material included descriptive statistics. Criteria $\chi 2$ were used to assess the significance of differences in qualitative features in unrelated groups. Differences between indices in varuous groups were considered significant at $p < 0.05$.

Research results and discussion: Diagnostic evaluation of the endometrium among women with pregnancy termination on the background of CP and anemia was made up of sonography, hysteroscopy and pathomorphology results. Sonographic study contributed to the stigma identification, indicating CE presence, the consolidation of which showed the possibility of selecting different types of inflammation (previously identified in the works that we have studied as hypo - and hyperplastic). Hysteroscopic features of chronic inflammation in the endometrium among women with termination of pregnancy on the background of EGD showed a high incidence of uneven mucosal thickness in a hyperplastic type (80.8% vs. 65.2%) ($p<0.05$). Hyperemia ± vascular mucosal injections were detected in 85.9% among women with the hyperplastic CE type and a quarter of patients had the hypoplastic one ($p<0.05$). Monovariance of signs was established in relation to pallor and thinning of the mucosa (in 76.0% with a hypoplastic CE type), polypoid outgrowths (77.8% – hyperplastic). Mucosal mosaicity was detected twice as often in the hyperplastic variant (40.4% vs. 22.5%) ($p<0.05$).

It is important to compare the diagnostic value of methods used in the assessment of the endometrial condition in order to substantiate the volume of examination of the contingent with pregnancy termination on the background of EGD (table 1).

The effectiveness of diagnosing the hyperplastic type complexly (using both sonography and visualization) was superior to that in the group with the hypo-

Diagnostic informational content of methods for detecting chronic endometritis

Groups	N	Sensitivity	Specificity	Diagnostic accuracy
Sonography				
Hypoplastic CE type	122	79,2	68,6	72,4
Hyperplastic CE type	188	92,6	66,7	78,9
Hysteroscopy				
Hypoplastic CE type	138	89,6	74,4	79,8
Hyperplastic CE type	198	97,5	77,2	86,7

plastic CE variant – for all analyzed constants.

Detailed endometrial histological studies in a group of women with early reproductive losses on the background of EGD showed the presence of endometrial polyps – 5.5%, intrauterine synechiae – 2.0%, unchanged mucosa – 9.3% (figure 1).

Pathological examination of endometrium in the sample with termination of pregnancy on the background of EGD proved that the combination of CE histostigmas was revealed in 83.5%, with a greater frequency of hypoplastic variants in CP (50.3% vs. 24.8% with anemia) (p <0.05) and the presence of the hyperplastic one – in half of the samples with anemia – in one and a half times more often (p <0.05). “Incomplete” morphological CE confirmation was determined in 39.2%.

Fibrosis of stroma and blood vessels was determined three times more often in the group with CP (83,2% versus 27.2%) (p<0.05). Infiltration of the endometrium by lymphocytes as a part of diagnosing chronic inflammation of the uterus was detected in 83.2% of mucosal biopsy specimens, diffuse “lesion” – one and a half times more often with anemia (p <0.05), follicular clusters – twice more often – with CP (p <0 , 05).

The discrepancy between the endometrial thickness and the MC phase on the background of chronic inflammation features was determined in 63.8% of the samples. Signs of productive inflammation in the interval of two months after pregnancy termination were found among 28.8% of women with EGD.

Women with the hypoplastic CE type were distinguished by the predominant presence of focal endometrial infiltration by lymphocytes – 4.6 times more often (72.1% vs. 15.8%) (p<0.05) along with dystrophic/atrophic endometrial transformation – with the same frequency (73.4%).

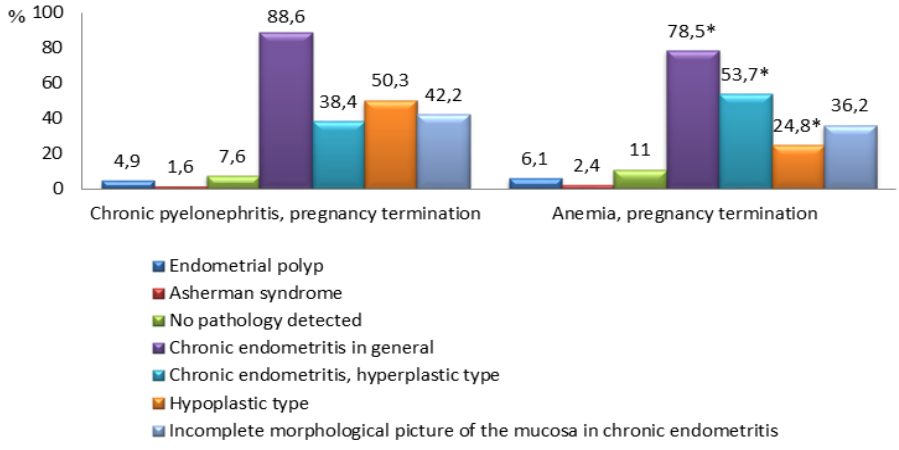

Fig. 1. Morphological characteristics of the endometrium in groups with EGD and pregnancy termination
Note: * (p <0.05) - differences are statistically significant between groups

Pathomorphological features revealed in the course of complex endometrial examination of women with CP and anemia have shown the possibility of reproductive losses prevention up to 83.5% by CE hypodiagnostics.

According to the data obtained, different effectiveness of evaluation methods of endometrial conditions among women with pregnancy termination on the background of CP and anemia shows their complementarity within the framework of distinguishing CE types which present the cause of reproductive losses in the early stages [7, 14].

Similar conclusions lead to the statement that improvement of women’s reproductive health is achieved by optimizing the diagnosis and the treatment of chronic inflammatory diseases of the pelvic organs [6].

The interrelation between the lack of pregravid preparation on the background of chronic EGD and high CE frequency is obvious. Their diagnosing and treatment on the pre-gestational stage seem to be the optimal prevention tactics of various violations of the “fetal-endometrial” interaction.

Thus, clarification of the concepts of CE pathogenesis in hypo- and hyperplastic types during a comprehensive study of women with abortion on the EGD background will allow for differentiated management tactics, involving a set of measures to restore the structural and functional viability of the uterine mucosa.

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ESTIMATION OF ANTIULCEROUS EFFECT OF MULTICOMPONENT PLANT EXTRACT IN EXPERIMENT

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ABSTRACT

The aim of the work was to estimate the antiulcerous effect of a new multicomponent plant extract derived from the following species of medicinal plant materials: leaves of *Plantago major* L., grass of *Gnaphalium uliginosum* L., rhizomes and roots of a *Inula helenium* L., flowers of *Matricaria chamomilla* L., roots of *Glycyrrhiza glabra* L., grass of *Polygonum aviculare* L., grass of *Urtica dioica* L., fruits of *Sorbus aucuparia* L.in the ratio 3:3:3:2:2:1:1:1. Standardization of the extract was carried out in terms of flavonoids. There was used the Pauls index (PI), the index of antiulcerous effect (AE) and morphological evaluation of the gastric mucosa. In experiments on *Wistar* line rats with butadion-induced injury of the stomach mucosa the marked antiulcerous activity of the multicomponent plant extract in a dose of 150 mg/kg has been established. The administration of the extract restricted the formation of ulcer defects which were more marked on the 14th and 21st days of observation. Such morphological features of activation of regenerative processes against the background of introduction of the given remedies as the new growth of vessels, cleanliness of the wound, inhibition of inflammatory reaction and active granulation were more expressed in rats treated with the extract and less distinct in rats treated with the preparations of comparison. The findings of the research confirm the expressed antiulcerous effect of the plant extract which is comparable to the effects of befunginum and ranitidine. The complex of biologically active substances contained in the extract promotes the acceleration of the ulcer healing due to its versatile influence on the main pathogenesis mechanisms of the given pathology. The findings of the research have shown that the tested extract has good prospects for creation of medicinal preparations for prophylaxis and treatment of gastric ulcer.

Keywords: multicomponent plant extract, model of the butadion-induced ulcer, antiulcerous effect.

Introduction. On abundance, weight of a current, complications and mortality the stomach ulcer occupies one of the leading places among diseases of the digestive system [7, 8]. In a disease pathogenesis the main role is assigned to balance upset between factors of aggression and protection of a mucosa of a stomach and duodenum against the background of change of a neuroendocrine and immune regulation of a gastroduodenal zone [4, 9, 11].

The market of medicinal preparations with the proved antiulcerous activity exceeds 500 names, at the same time the problem of effective therapy is far from the permission. At treatment antiulcerous tools observe development of aggravations and emergence of a recurrence in 30-80% of cases, the complicated stomach ulcer forms meet at 25-45% of patients, the resistance of gastroduodenal ulcers to pharmacotherapeutic influence meets at 15-25% of patients, the side reactions at reception of a number of medicines are observed at one third of patients. Therefore relevant is a problem of development of the effective, not having the side effect gastroprotectiv tools [3, 6, 10].

In this regard, the purpose of our research was determination of antiulcerous activity of new complex plant extract.

Materials and research methods. As object of researches served extract dry, received from the following types of vegetable raw materials: leaves of *Plantago major* L. (3 h), grass of *Gnaphalium uliginosum* L. (3 h), rhizomes and roots *Inula helenium* L. (3 h), flowers of *Matricaria chamomilla* L. (2 h), roots *Glycyrrhiza glabra* L. (2 h), grass of *Polygonum aviculare* L. (1 h), leaves of *Urtica dioica* L. (1 h), fruits of *Sorbus aucuparia* L. (1 h). The received extract contains carotenoids,

polysaccharides, flavonoids, tanning agents, saponin, steroids, proteins, sesquiterpene lactones, mucilage's, pitches, organic acids, vitamins, macro - and minerals, essential oils and other natural connections. Standardization of extract is carried out on the sum of flavonoids.

Work is performed according to "The guide to carrying out preclinical researches of pharmaceuticals". Experiments are executed on 104 white rats males of the Wistar line with an initial weight of 180-200. Animals received from "Scientific center of biomedical technologies" and contained in conditions of the certified vivarium with the free access to a forage and water. Pharmacological researches were conducted according to "Rules of work with use of the experimental animals", "The rules adopted by the European convention on protection of the vertebrate animals used for the experimental and others scientific". Keeping of animals and design of researches are coordinated with ethical committee.

Beforehand on model of stressful ulcers experimental and therapeutic doses of the received extract with use of the antiulcerous index of Pauls which corresponded to 100-350 mg/kg are defined. Doses of 400 mg/kg had also above no advantages therefore all subsequent experiments are made with use of a dose – 150 mg/kg.

Antiulcerous activity of an aqueous solution of complex plant extract studied in an experimental and therapeutic dose 150 mg/kg and comparison medicines: in isoeffective doses befunginum (0.3 ml/kg) and ranitidine (50 mg/kg).

The antiulcerous activity of extract was studied in the conditions of model of "a butadion ulcer". White rats in this experiment were distributed on groups: intact (8 rats); control (24 rats); experienced 1 (24 rats); experienced 2 (24 rats); experienced 3 (24 rats). The canker mucous a stomach was reproduced intraperitoneal introduction of butadionum in a dose by 100 mg/kg of 1 times a day within 3 days in a row. From the fourth day to skilled groups 1, 2, 3 entered into a stomach extract, befunginum, ranitidine in the specified doses, respectively, 1 times a day within 10 days. In monitoring to rats entered an equivalent amount of water cleaned in the similar mode. Intact animals served as additional monitoring. The euthanizing of animal skilled groups 1, 2, 3 and monitoring was carried out for the 7, 14 and 21 day since the beginning of experiences in CO_2 to the camera. After opening of animals measured the area of ulcer defects in mm^2 and also calculated the index of antiulcerous effect of the studied extract and reference medicines [5, 8]. The Pauls's Index (PI) was calculated on a formula: PI =A*V/100, where A – average quantity of ulcers on one animal; V – quantity of animals with ulcers in group. About the antiulcerous action (AA) of extract judged by the relation of PI in monitoring to PI in skilled group of animals (AA = PI c/ PI e); at AA= 2 and more considered that extract and also reference medicines have antiulcerous effect [4.8].

Morphological researches of a stomach were conducted for the 7, 14 and 21 day since the beginning of experiences. For these purpose stomachs of rats fixed in 10% solution of neutral formalin, filled in in paraffin, prepared cuts 5 microns thick and painted a hematoxylin and eosin [8]. By means of a microscope of Axiostar plus (C. Zeiss) estimated a condition mucous, submucous and muscular layers, expressiveness of inflammatory reaction and activity of regenerator processes.

1. Statistical processing of the obtained data was carried out with use of the Statistic 6.0 software package (USA). The importance of differences between selections with the distribution coming to normal was estimated by means of "t" - a criterion of Student [1]. Distinctions accepted significant at P≤0.05.

Results and discussion. Influence of the received multicomponent plant extract on the course of butadion stomach ulcer at white rats is studied.

Apparently from the data provided in table 1, introduction of extract limits the formation of ulcer defects which is most expressed for 14 and 21 days of experience. Reference medicines also reduced the sizes of cankers mucous a stomach, conceding by efficiency to extract. The expressed antiulcerous effect of extract on late lines of a course of pathological process, apparently, is caused by mucous accelerated by regeneration of an epithelium.

The index of antiulcerous effect of extract corresponds to 3.4; at introduction of befunginum – 2.5; and at ranitidine introduction it corresponds 2.0 (table 2).

Histologically in this experiment it is established that for the 7th day in monitoring the deep ulcer defect filled with necrotic masses is found (a desquamated epithelium, clots, mucilage's), around an ulcer of a fold mucous are thickened, infiltrate leukocytes. Edges of defect irregular, the expressed hypostasis and infiltration of mucous and submucous layers is observed by granulocytes, found lymphocytes in a small amount. Far from ulcer defect numerous erosion are visible. Against the background of introduction of extract at animals of skilled group 1 in an infiltrate of mucous and submucous lymphocytes dominate, folds mucous are hydropic, hyperemic, the extent of defect it is much less, than in monitoring, and around an ulcer found single erosion and dot hemorrhages. In skilled groups 2 and 3 also the extent of ulcer defect was less, than at rats of control group, observed also hypostasis and infiltration of mucous and submucous layers mainly leukocytes.

For the 14th day of an experiment at rats of control group the extensive and deep defect with a necrotic masses remained, the stomach wall in the field of an ulcer is thickened, infiltrate, the expressed inflammatory reaction with hypostasis of all layers was observed. In infiltrate macrophages, fibroblasts are already noticeable. At the bottom of an ulcer found new growths of vessels, hypostasis and the expressed hyperemia remained. Mucous pieces of iron were found in edges of an ulcer. In skilled group 1 processes of the fissile adhesion of defect with the granulation filling ulcer cavities are noticeable sites of an integumentary epithelium with the high content of mucilage are found. Against the background of introduction of reference medicines observed a similar trend with less expressed activity of regenerator processes.

21 day of experience in control group

Table 1

Influence of extract on ulcer defects at «butadion» stomach ulcer at white rats

Groups of animals	Area of ulcer defects, mm2		
	7 days	the 14th day	21 day
Intact	0	0	0
Control	84,2±2,30	69,8±2,80	51,6±2,10
Experienced 1	66,1±1,20*	46,8±1,60*	14,2±1,00*
Experienced 2	72,5±1,30*	48,0±1,70*	20,8±0,90*
Experienced 3	70,3±1,00*	51,0±1,10*	25,2±1,00*

Note: hereinafter * - distinctions are significant at P≤0.05.

Table 2

Influence of plant extract on the course of «butadion» stomach ulcer at white rats (21 day of experience)

Groups of animals	Quantity of rats with ulcers, %	Quantity of destructions on 1 rat	PI	AA
Intact	0	0	0	0
Control	100	12,6±0,68	12,6	0
Experienced 1	50	5,5±0,21*	3,7	3,4
Experienced 2	80	6,0±0,24*	5,0	2,5
Experienced 3	78	7,5±0,22*	6,2	2,0

of rats later observed the phenomena of partial clarification of ulcer defect from necrotic masses, hypostasis of all layers of a wall remains, a damage zone hyperemia is noticeable. In skilled group 1 processes of the fissile regeneration in a defect zone clearly are noticeable, seams practically filled defect, but the complete recovery mucous is noted that it is probably bound to a short course of introduction of extract. In groups with introduction of befunginum and ranitidine strengthening of reparative processes, and, more the first in morphological features in skilled group 2 - against the background of introduction of befunginum is also noted. The complete adhesion of ulcer defect with restitution mucous is also noted at animals.

Thus, the studied extract, befunginum, ranitidine have antiulcerous effect. The greatest activity is shown by extract in connection with existence in it of a wide range biologically of the active materials providing the fissile cell regeneration mucous and reducing the damaging action of butadionum at white rats that is bound apparently, with ability of the received extract to inhibit activity of cyclooxygenase 1 and 2 with the subsequent decrease in synthesis of prostaglandins [2, 4].

Conclusion. In general, data of the conducted researches confirm the expressed antiulcerous effect of the studied plant extract which is comparable to effects of befunginum and ranitidine in experiences on rats with damages mucous a stomach. Course introduction by an animal of extract and reference medicines in isoeffective doses is characterized by natural decrease in the index of Pauls and increase in the index of antiulcerous action – the main criteria of antiulcerous activity of medicinal preparations. The new growth of vessels, early clarification of a wound, restriction of inflammatory reaction, the fissile granulation which were more expressed when using extract were morphological features of activation of regenerator processes against the background of introduction of the specified tools. Rich complex biologically of the active materials which are available in extract promotes acceleration of an adhesion of ulcer defect thanks to its multilateral influence on the main pathogenesis mechanisms of a peptic ulcer. In fact, the system influence of extract counterbalancing factors of aggression and protection at its application that will be coordinated with literary data [5, 11] is considered. The received results demonstrate antiulcerous effect of complex plant extract and are of great interest to clinical practice, reason expediency of its application as a part of the used technologies of treatment of patients with a peptic ulcer and also at the recovery stage that will increase effectiveness of the held treatment-and-prophylactic events.

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ANALYSIS OF MICROCIRCULATORY DISORDERS IN PATIENTS WITH LICHEN RUBER PLANUS OF ORAL MUCOSA

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ABSTRACT

At the dental appointment, there is an increasing frequency of lichen planus in the oral cavity. In this case, erosive-ulcerous form of lichen planus is one of the most common and difficult to treat. At present, issues of aetiopathogenesis of lichen ruber planus in geriatric dentistry are not yet clear. In this work, development of inflammatory-destructive diseases is dealt with from the standpoint of microcirculatory disorders in patients' oral cavity. To study microcirculatory changes in patients with erosive ulcerous form of lichen ruber planus, a comparative analysis of microcirculatory component and amplitude-frequency spectrum was carried out in patients with this pathology with respect to a group of healthy people aged 45-59.

Material and methods. Microcirculation was studied with Doppler laser flowmetry in 60 patients in comparison with healthy people (30 people).

Results. Hemocirculatory disorders were revealed in patients both on the side of pathology and in the symmetric area, which indicates systemic microcirculatory changes in the oral cavity.

Discussion. The data obtained suggest that it is advisable to perform laser Doppler flowmetry prior to and against the background of pharmacotherapy.

Conclusion. In inflammatory-destructive lesions of the oral mucosa, increased microcirculation parameters against the background of decreased average perfusion fluctuation and vasomotor activity of the vessels is observed. The amplitude-frequency spectrum, carried out by wavelet transform, showed a decrease in the amplitude of low-frequency flaws and an increase in the amplitude of pulse and respiratory waves. Endothelial oscillations decay probably occurs against the background of decreased synthesis of nitric oxide; as the frequency range of secretory activity of the endothelium and synthesis of nitric oxide coincide in the microcirculatory bed, functional relationship between these parameters can be traced. Vasomotor rhythm decline, vasoconstriction of the vessels, decrease in endothelial oscillations amplitude indicate endothelial dysfunction. Having high sensitivity to changes in the microhemodynamic situation in the vascular bed, the use of LDF makes it possible to evaluate the state of functioning of control mechanisms and is a valid method of application in gerontostomatological practice.

Keywords: microcirculation, Doppler, erosion, ulcer, regeneration, therapy.

Introduction. With a large variety of inflammatory-destructive diseases of the oral cavity, lichen ruber planus (LRP) is one of the most common in geriatric dentistry, especially its erosive-ulcerous form prone to malignization and chronic forms [1, 7, 12]. The disease can develop at any age [5, 13]. At present it is impossible to say at what age this disease is most common but there is a clear tendency towards increase of this pathology among young people [18, 16]. It may happen due to lower immunity, as well as to psychogenic factors (the pathology develops as sympathoadrenal type), microcirculatory disorders and naturally due to predicting factors in the oral cavity – chronic infections, sharp teeth edges, fillings leading to injuries of the oral mucosa, damaged integrity of the epithelium of the oral mucosa [14,15]. In this connection it is important to carry out additional methods of diagnosis, reveal a provoking factor at an early stage that can lead to development and frequently to recurrence of the pathology and, as a result, timely modern and aetiopathogenetic chemotherapy [6, 11, 13].

LRP genesis is not clearly defined so far [3]. For this reason, there is no clear approach to chemotherapy of the pathology. Existing methods and therapeutic agents are only of symptomatic character and do not affect periods of remission and exacerbation [2, 12]. With a wide range of innovative methods of diagnosis and LRP treatment, there is always a question arising in geriatric dental practice: how reasonable is to prescribe this or that medicine which is effective not only at the local but also at the systemic level. In inflammatory-destructive diseases changes in hemodynamics occur, such as vascular permeability disorders, hypoxemia, angiospasm, atony, etc. To diagnose pathophysiological condition of the microcirculatory bed one should analyze active (factors affecting microcirculation system) and passive (factors affecting blood flow from without) mechanisms regulating capillary blood flow in the oral cavity [2, 10]. For this purpose application of laser Doppler flowmeter (LDF) based on Doppler effect; short-wave probe laser radiation makes it possible to get an echoed signal of a large amplitude from individual erythrocytes forming a thin layer of about 1 mm containing elements of the hemomicrocirculatory bloodstream [6]. This method helps obtain the maximal information on disorders in regulatory blood flow mechanisms in the microcirculatory bed which require correction [4, 9].

The **objective** of this article is analysis of regulation mechanisms of microcirculation in the oral mucosa in patients with lichen ruber planus with respect to normal people with the help of laser Doppler flowmeter.

Material and methods. To achieve the purpose, 60 patients with erosive-ulcerous lichen ruber planus of the oral mucosa at the age from 45 to 59 were examined.

On clinical examination of the patients special attention was paid to the color of oral mucosa (development and blood filling of small vessels), thickness and transparency of epithelium, presence of corneal layer and cornification degree, content of mucosa pigments (endogenous – melanin, exogenous – "amalgam tattoo", etc), surface, density and OM mobility (papillae, folds, depressions)

Carrying out LDF one should consider the following factors which can affect microcirculation parameters: menstrual cycle, physical activity, psychoemotional tension, body temperature) Capillary blood flow was analyzed in all parts of the oral mucosa, doing this a transducer was placed not only on erosions and ulcers but also on intact oral mucosa without any defects of epithelium.

All patients were randomized into 3 groups: experimental group I – study of microcirculation parameters in erosive-ulcerous areas, experimental group II – oral mucosa without signs of epithelium damage, control group III группа – normal people without any accompanying pathology.

Study of LDF- images was conducted in accordance with the protocol in two

stages [3]: in the first stage basal blood flow was studied and in the second stage – blood flow oscillation by wavelet transformation. As a conclusion the forma and degree of microcirculation disorder was shown.

The obtained data were processed using variational-statistical method Statistica 6 application package (Statsoft-Russia, 1999) and Microsoft Excel Windows 2000. Statistical analysis was done with variational-statistical method by determining mean (M), its mean error (±m), evaluation of significance of differences by group with Student's test (t). Difference between compared indicators was considered to be significant with $p< 0.05$, $t\geq 2$.

Results and discussion. In the group of healthy people (III) LDF helped to reveal regulatory parameters of microcirculation in the buccal mucosa: microcirculation parameter (MP) was 22.81±0.51 perf.units; SD was equal to 5.24±0.34 perf. units. and coefficient of variation (CV) was 23.0±0.12%.

Endothelial fluctuations amplitude made 1.73±0.15 Hz, neurogenous – 1.39±0.13 Hz, myogenous – 2.66±0.2 Hz, respiratory and cardiac – 0.79±0.09 Hz and 0.17±0.05 Hz accordingly. Thus, in the group of normal people endothelial and myogenous flux motion prevail. Analysis of standardized characteristics of fluctuation rhythms, that is fluctuations amplitude contribution relative to the average blood flow modulation in the control group showed that vasomotor rhythm was dominant (VLF – oscillations – 25%; LF_H – oscillations – 21%; LF_M – 39%; HF – 12%; CF – 3%). Shunting value that enables to evaluate the influence of myogenous, neurogenous and endothelial components of microvessels made 0,7±0,12 Hz, that is the evidence of dominant oscillations of endothelial and myogenous rhythms. Thus, it is possible to conclude that in the oral cavity of healthy people of the III group mesoemic type prevails, characterized by average parameters of tissue blood flow and well marked aperiodicity of oscillations in LDF.

On interpreting the results of the I group, the following values were obtained characterizing marked impairment of capillary blood flow in the bloodstream. The mean value of MP was equal to 31,68±0,55; flux level - 1,87±0,03; vasomotor activity of microvessels made 5,5±0,17%. Significant decrease in CV by 4.2 times was noted in patients with LRP that is the evidence of decreased speed of the local blood flow, vasoconstriction, deterioration of microcirculation comparing with normal people. On the symmetrical side of the oral cavity in patients with LRP CV was also 3.5 times lower (6,57±0,14% and 23,0±0,12%, with $p<0,05$). Naturally, the value of average perfusion oscillation relative to the mean value of blood flow also dropped (σ – 2,06±0,04 perf. units), the value of the average blood flow made 31,37±0,1 perf. units, that is the evidence of increased blood volume in arterioles. Changes in microcirculation parameters in the basic part of the study in relation to the control group characterizes decreased vasomotor vascular activity in the oral cavity in LRP patients independent on localization of pathologic elements.

Rhythmic structure of blood flow oscillations also changed – the amplitude of low-frequency oscillations became lower due to the weaker vasomotor rhythm. So, the amplitude of endothelial oscillations in the area of erosive-ulcerous lesions was 82,1% lower comparing to the control group and was equal to 0,95±0,16 Hz, neurogenous - 39% - 0,97±0,27 Hz. Flux motion of myogenous oscillations were also lower (0,90±0,28 Гц) and the amplitude of high-frequency flux motions, the pulse wave in particular, was 82,3% higher and made 0,31±0,06 Hz, respiratory wave amplitude was equal to 0,5±0,2 Hz. By contribution correlation of active and passive flux motions the amplitude of LF – oscillations was – 35%; VLF – 26,5%; HF – and CF – oscillations – 17,5% and 21% accordingly. Shunting value made 1,32±0,2 Hz.

Study of blood flow in the patients with LRP on the symmetric side also revealed significant difference in characteristics comparing to the control group but no significant difference was revealed comparing to group I. The level of LDF- signal on the symmetrical side of the buccal mucosa underwent serious changes in relation to the control group. So, MP in group II was 31,37±0,1 Hz, that was significantly higher than in the control group - 18,32±1,02 Hz. СКО made 2,06±0,04 Hz, that was significantly lower comparing to group III, CV – 6,57±0,14%, that is twice lower than in the control group. In LRP patients contribution of passive oscillations (pulse and respiratory wave) was also noted on the symmetrical side of the cheek. On the buccal mucosa it grew 1,5 times larger comparing to the control group.

Discussion. The data obtained by laser Doppler flowmetry showed that patients with erosive-ulcerous lichen ruber planus were characterized by lower vasomotor vessel activity, lower blood flow, vasoconstriction of blood vessels, significant decrease in the amplitude of low-frequency oscillations accompanied by endothelial disfunction in the oral cavity.

Impairment of microcirculation in the oral cavity are rather uniform both in the lesion focus and on the symmetrical intact side. Local spasm of arteriolar vessels, hypoxemia in microcirculatory bloodstream, lowered intensity and speed of blood flow in the capillaries was noted in the oral cavity. It should be noted that microcirculation impairment in the oral cavity is impossible to compare to any specific form. he main tendencies of changes of LDF values correspond to the hyperemic form. Microcirculation value is above normal, flux is decreased, the amplitude of vasomotor waves is reduced and the amplitude of the respiratory and especially of the pulse wave is considerably higher, variation factor is below normal. Monotonous type of LDF-image with high perfusion (hyperemic) is characterized by a high perfusion value and monotonous fluctuations of tissue blood flow due to low flux and CV values. In this case, a considerable contribution of respiratory and pulse components alongside with a lower tone of vasomotor fluctuations is the evidence of relative weakening of sympathetic influence.

Degree of microcirculatory changes depend on the intensity of the process. Microcirculation impairment is largely expressed in the lesion foci of cheeks and lips mucosa. These changes in the rhythmic structure of flux motion become more evident as blood flow and microcirculation impairment get worse. It means that the lower is contribution of vasomotions to the active modulation of microcirculatory hemodynamics, the larger is compensatory role of other regulatory mechanisms. With inflammatory-destructive process in the oral mucosa, vascular impairment of the microcirculatory bloodstream develop early manifesting in venous congestion, slower metabolism reduced vasomotor vascular activity, slower local blood flow. A topical issue is to reveal those elements in the pathogenic mechanism of microcirculatory impairments in oral mucosa diseases; acting on them will reduce the level of microcirculatory impairments and improve trophism of oral mucosa, which in turn should be taken inti consideration treating this pathology.

Conclusions. Analysis of the data obtained showed that correlation of rhythmic components in LDF-image objectively reflects condition of hemodynamics in the microcirculatory bloodstream of LRP patients.

Against the background of general spectral narrowing of LDF-image, the patients show evident suppression of vasomotor rhythm, increased high-frequency oscillations, especially in the area of cardiac rhythm. A higher degree of manifested microcirculation impairment is observed in the lesion focus of buccal mucosa. Changes in the rhythmic structure of flux motions are expressed more clearly as blood flow and microcirculation impairment get worse. It means that the lower is contribution of vasomotions to the active modulation of microcirculatory hemodynamics; the larger is compensatory role of other regulatory mechanisms. The amplitude of endothelial oscillations decreases due to reduced synthesis of nitric oxide, as the frequency range of endothelial activity and NO synthesis coincide in the microcirculatory bloodstream. The amplitude of myogenic oscillations probably decreases due to calcium metabolism disorder that participates in muscular contraction of blood vessels. In this case, nitric oxide synthesized by endothelium diffuses to myocytes and with their deficit calcium metabolism is impaired resulting in vasoconstriction of blood vessels. Drop in amplitude of neurogenous oscillations is associated with sympathetic adrenergic influence, адренергическими влияниями and as this occurs, sympathetic vasomotor activity increases resulting in compensatory vascular constriction. Thus, it is logical to detect microcirculatory changes in inflammatory-destructive dental diseases with LDF which in combination with clinical data permits to receive a complete picture of impaired tissue condition.

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ADDITIONAL DIAGNOSTICS METHODS FOR THE PLANNING OF PREVENTION OF DENTAL CARIES AND ITS COMPLICATIONS IN CHILDREN

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ABSTRACT

Temporal teeth caries and its complications, among other unsolved global problems, are relevant in the Khabarovsk Territory. A survey of 885 children 3 and 6 years old in the Khabarovsk Territory showed a high prevalence of dental caries: at 3 years up to 70.8% ± 1.1% and at 6 years old - 89.4% ± 1.3%, with an intensity of affecting children 3 3.34 ± 0.09 years, by 6 years old 6.4 ± 0.9 teeth. Pulpitis is 61.7% ± 1.1%. Determination of the density of bacteria S. S. mutans of dental plaque from the four surfaces of the teeth, the mucous membrane of the tongue and saliva was done by the microbiological method using Dentocult SM Strip Mutans. High contamination of S. mutans of dental plaque from the lingual surface of the tooth and interdental space, with a titer of CFU / ml>106, the lowest content of S. mutans in the saliva is CFU / ml 105. We conducted a microscopic study of the native scraping from the root of the tongue, revealed signs of chronic dehydration of the oral mucous membrane, and established its direct strong correlation with the caries, filling, extracted/removed tooth (CFR) index (r = 0.723, p = 0.013). Microcrystallization of oral fluid (MOF) was assessed, in frequently ill children, type II of the MOF (subtype B and C) is found in 70% ± 2.7% and type III of the MOF in 26.4% ± 2.7%. Additional innovative microbiological and microscopic methods personify the approach to the diagnosis, prevention and treatment of caries in children of early and preschool age, have prognostic value and allow taking into account regional features.

Keywords: epidemiological, microbiological and microscopic studies, caries of temporary teeth, pulpitis, children, cariogenic bacteria, chronic dehydration.

Introduction. According to the WHO, the prevalence of infectious diseases of dental caries in different countries reaches 94%. The actual and still unsolved problem of children's dentistry is caries of temporary teeth and its complications [2, 7, 9, 12, 14]. The main factors of initiation and development of caries are known: the presence and high titer of cariogenic bacteria *Streptococcus mutans* and *Streptococcus sobrinus* [2, 10, 13], a low level of practical skills in oral hygiene [4], changes in the composition and properties of the oral fluid [1, 8], uncontrolled consumption of sugars [11], low hygienic / sanological culture of parents [6], complicated during pregnancy [6, 11], which makes it possible to identify dental caries as a multifactorial polyetiological disease and an opportunistic infectious process [2]. In Eastern European countries, the caries of the teeth of children under 6 years old is 56.9% [5], in the Asian region up to 85% [5], in Russia for children 3-6 years old it is from 36% to 87%, with an average intensity 2,8 and 4.7 teeth [4, 9], in 80% of patients complicated forms are determined [8]. Thus, the most effective correction of dental status in children is possible when identifying the leading risk factors for the development of caries and pulpitis, taking into account regional features.

Objective: to introduce additional innovative diagnostic methods for the planning of primary prevention of caries of temporary teeth in children.

Materials and research methods:

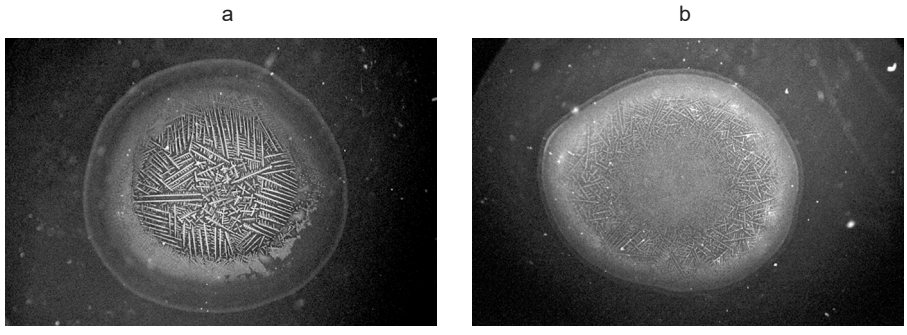

Fig.1. Evaluation of microcrystallization of the oral fluid: a. - II type (subtype A) of the MOF; b. - III type of MOF

Colonization of biotopes of the oral cavity of *S. mutans*

Species of bacteria	Oral cavity biotope	Class of seeding	Titer CFU/ml
Streptococcus mutans	Tongue surface of teeth	2,27±0,09**	>106
	Surface of tongue	2,27±0,09**	>106
	Interdental space	2,17±0,09*	>106
	Vestibular surface	2,10±0,11*	105-106
	Occlusal surface	2,10±0,10*	105-106

Note. Differences are statistically significant at * p = 0.05, ** p = 0.01, calculated with respect to saliva.

a survey of 885 children 3 and 6 years old living in the Khabarovsk Territory was conducted. Informed consent was obtained from the parents in accordance with Art. 20, №323-the Federal Law dated 11.21.2011. The research program, the questionnaire, the informed consent of the parents was approved by the Ethics Committee of FESMU on March 28, 2018. In the course of the epidemiological dental study we estimated prevalence and intensity of caries of temporary teeth and pulpitis, the structure “caries, filling, extracted/removed tooth” (CFR) for children under 3 years of age and “caries, filling, extracted/removed tooth” from among permanent teeth + caries and filling of temporary teeth (CFR + cf) for children with replaceable bite. The level of oral hygiene (HL) was determined by indices: 3 years by E. M. Kuzmina (2000); at the age of 6 according to Fyodorov-Volodkina (1968). Caries genicity of dental plaque (CGP) was detected by the method of Hardwick-Manley (1952), modified by T. G. Petrova. Microcrystallization of saliva / oral fluid (MOF) was assessed by the method of wedge dehydration according to VN Shabalin and S. N. Shatokhina (2001).

Additional innovative diagnostic methods were introduced: microbiological determination of the presence and density of *S. mutans* contamination of four surfaces of intact areas of the teeth, tongue mucosa and saliva (Patent for the invention of the Russian Federation 2661609, 17.07.2018). The degree of colonization of the oral cavity was evaluated by the culture method according to the instructions “Dentocult SM Strip Mutans”, “Vivadent”, and compared with a reference card, distributed into classes in accordance with CFU / ml. For a microscopic study of dehydration of the mucous membranes of the oral cavity (MMOC), a native tongue scraping (Patent for the invention of the Russian Federation 2668498, 01.10.2018) stained by Gram was investigated [3]. In order to identify the presence or absence of postnatal risk factors for the development of dental diseases in children, a sociological survey of parents on the developed questionnaire was conducted.

Data analysis was performed using the statistical software package Statistika 10.0. Student’s t-criterion, the exact criterion of Fisher’s χ^2 were determined, the Pearson criterion, the Chaddock’s scale were used.

Results and discussion. According to the epidemiological study, in the Khabarovsk territory the prevalence of dental caries in 3 years old was 70.8% ± 1.1% and in 6 years old - 89.4% ± 1.3%, p = 0.001, which by criterion WHO corresponds to a high level, with an intensity of lesion in children 3 years old 3.34 ± 0.09, to 6 years old 6.4 ± 0.9 teeth, p = 0.001. Pulpitis accounts for an average of 61.7% ± 1.1% of cases. Analysis of the structure of cfr and CFR + cf showed the predominance of the component “c”: in 3 years to 2.1 teeth and at 6 years - an increase to 4.8 affected teeth. A direct strong connection between the ct and HL of the oral cavity was revealed: with a single lesion, the hygiene level is satisfactory and is 0.3 ± 0.01 in infants, 1.4 ± 0.03 in preschool children; in the case of multiple caries, a poor HL predominates - 0.93 ± 0.01 in 3 years old; and in 6 years old - 2,1 ± 0,2 - unsatisfactory (r = 0,97; p = 0,011). This is due to the low level of hygienic knowledge of parents, which is confirmed by a sociological survey: 47% ± 1.3% of the children polish their teeth once a day and 58% ± 2.1% twice a day, p = 0.001. This is due to the low level of hygienic knowledge of parents, which is confirmed by a sociological survey: 47% ± 1.3% of the children polish their teeth once a day and 58% ± 2.1% twice a day, p = 0.001. 69.2% ± 1.27% of mothers are introduced into the baby’s diet sweet food in 1 - 2 years. The later the child was introduced sugar-containing products, the lower the indicator of the intensity of dental caries (r =-0.40, p = 0.01).

Sweetened drinks and juices for the night give 26.97 ± 3.12% of parents - these children are characterized by a direct strong correlation with a high cfr index (r = 0.82, p = 0.01), low level of practical hygiene skills oral cavity (r = 0,61, p = 0.05) and pronounced CGP (r = 0.41, p = 0.05). In children with low caries resistance in 43.5% ± 2.1% of cases, an unsatisfactory level of hygiene was recorded, which causes aggressive

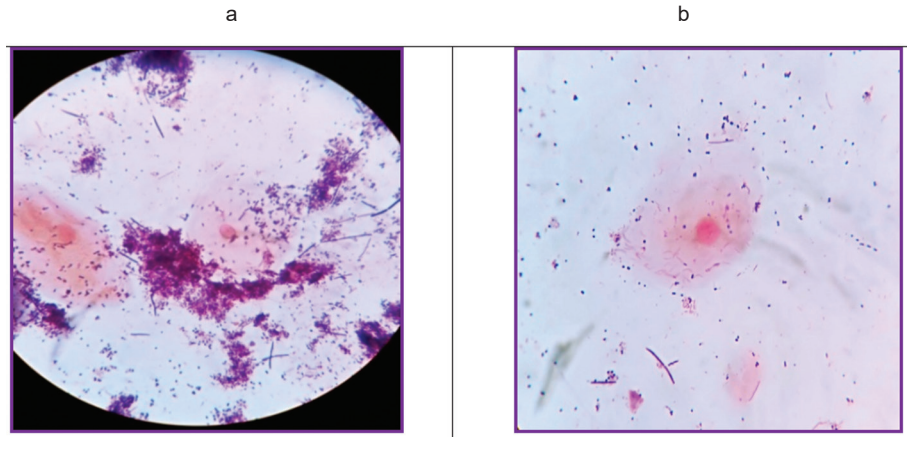

Fig. 2. Native scraping from the root of the tongue (Gram method, microscopy with immersion, magnification ×1500): a - signs of chronic dehydration, b – normal view

caries in 37% ± 1.3% of children in the Khabarovsk territory (r = 0.61, p = 0.01).

The presence of abundant dental plaque and its cariogenicity play a leading role in the initiation and progression of caries of temporary teeth in children: a pronounced CGP with multiple caries - 2.64 ± 0.6 and a low CGP - 1.3 ± 0.01, (r = 1; p = 0.01) with single lesions of temporary teeth.

The evaluation of the MOF revealed types that depend on the degree of caries activity and the somatic status of children: I type of MOF in 45.5% ± 1.3% cases and type II (subtype A) prevailed in 23.5% ± 1.7% cases of the examined (Fig. 1, a) with single lesions of caries and absence of somatic pathology.

In frequently ill children, the saliva structure changes (Figure 1, b): in 70% ± 2.7%, type II of the MOF is determined (predominantly subtype B and C) and 26.4% ± 2.7% of cases III type of MOF.

An analysis of microbiological studies of biotopes of the oral cavity (Table) showed high contamination by *S. mutans* bacteria on the surface of the tongue, dental plaque from the lingual surface of the tooth and the interdental space and their greatest informative value, with a CFU / ml>10^6 / ml titer, and the lowest *S. mutans* in saliva - CFU / ml <10^5 (p = 0.001), when compared.

The revealed maximum contamination of *S. mutans* of the tongue surface of the teeth and the tongue has a prognostic value: when planning a program of prophylaxis, it should be borne in mind that the tongue can serve as a place of constant donation of pathogenic/ cariogenic streptococci.

Microscopic examination of native scrapings from the root of the tongue (Fig. 2 a, b) revealed signs of chronic dehydration of MMOC in children, established its direct strong correlation with the index cfr (r = 0.723, p = 0.013): in 85% ± 2,6% with decompensation of caries recorded a variety of clusters of microorganisms, their pronounced co-adhesion, so-adhesion and histadhesion; insufficient volume and high viscosity of saliva (Fig. 2, a) while, according to the survey, 40.7% ± 1.7% of children prefer juices and compote, and drinking water is less than 10% ± 0.9% of the subjects. Children who observe water drinking regimen have a lower rate of formation of dental plaque; smears show a low degree of co-adhesion, so-adhesion and histadhesion, no accumulation of microbes and viscous mucus (Fig. 2b).

Conclusion. Thus, a survey of children of early and preschool age showed a lack of regular rehabilitation, a high titer of pathogenic *S. mutans* in dental plaque, a low level of knowledge of oral hygiene, chronic dehydration of the MMOC and pronounced cariogenic of dental plaque. The results of a sociological survey of parents indicate an insufficient level of their hygienic knowledge, the use of unbalanced nutrition of children with a predominance of sugars. Low preventive activity and lack of parental control dictates the need to intensify programs aimed at increasing their compliance and sanological culture. Our study showed a high prognostic value of additional innovative research methods, which allows us to recommend them for a broad introduction and personalized approach to the program for the prevention of caries and its complications in children.

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HEALTHY LIFESTYLE. PREVENTION

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PREVALENCE OF SMOKING AMONG ADOLESCENTS OF YAKUTSK

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ABSTRACT

The article focuses on smoking - one of the most common bad habits spread among the major part of the world’s population. Tobacco use is one of major risk factors for a number of chronic diseases, including cancer, lung and cardiovascular disease. A number of countries had adopted laws restricting tobacco advertisement, establishing a circle of persons who can buy and consume tobacco products as well as regulating smoking areas. It is proved that the respiratory system (larynx, trachea, bronchial tube, lungs) is more affected by regular intake of nicotine. That is why almost every smoker has problems with his lungs, bronchi or trachea. The aim of the research is to study prevalence of smoking among adolescents in Yakutsk. The study was conducted by a representative sample of Yakutsk schoolchildren with the use of a random number generator. 6 schools were selected from the list of all general education institutions of the city. 931 students of grades 8-11 aged 13 to 17 took a voluntary participation in the survey, among which 57,3% are boys, 42,7% are girls respectively. According to the results of the survey, the prevalence of tobacco consumption among schoolchildren in Yakutsk was 41,5%, among which 39,6% are boys, 44% are girls. Proportion of children with experience of smoking by the age 15-17 is 2.6 times higher than the indicators of a group of children aged 13-15, which indicates sustainable formation of tobacco dependence among adolescents of this age. Analysis on number of cigarettes consumed per day revealed that 71% of boys and 65% of girls smoked up to 5 cigarettes per day; 18% of boys and 30% of girls smoked from 5 to 10 cigarettes per day; 5% of children consumed 10 and more than 12 cigarettes respectively. Among occasional smokers 18% of children smoked 5 and more cigarettes per day. To fight against smoking among adolescents integrative approaches are required combining both preventive and special programs using age-appropriate modern methods of rehabilitation.

Keywords: children, adolescents, Yakutsk, Yakutia, smoking, tobacco smoking.

Introduction. According to the World Health Organization (WHO), tobacco smoking claims the lives of nearly 7 million human annually, of which more than 890,000 are passive smokers [8]. According to many authors in recent years, cigarette consumption among adolescents has increased. Thus, the average rate of cigarette consumption for

all countries is 12% boys and 11% girls on average [13].

According to the 2015 WHO report on the global tobacco epidemic, in Europe 19% of women at the age 15 and older consumed tobacco. This indicator is high in comparison with the equivalent figure in other WHO regions - Africa, South-East Asia, the Eastern Mediterranean and the West Pacific region, where it fluctuates within 2-3% [7].

In our country the prevalence of tobacco smoking among different population groups remains high, which poses a serious threat to public health in the near future. According to many authors, on average 65% of men and up to 30% of women consume tobacco, thereby smoking in Russia is the most common bad habit. It should be noted that among young and less educated population of Russia the prevalence of smoking is even higher. Tobacco smoking is one of the main factors in the development of many chronic diseases and related complications which lead to loss of function, disability and death [2, 4, 5, 10].

According to sample social survey, the proportion of smoking children and adolescents is growing in Russia. In Moscow about 40% of boys and 30% of girls smoke, in Yakutsk it is 34 and 40%, in Tula 40 and 32% respectively, in Voronezh is it more than 50% of adolescents. And if 60-70% of children smoke 1-5 cigarettes, the rest smoke 10 and more cigarettes [6]. According to S.Yu. Artamonova in Yakutsk among adolescents consuming tobacco 77,2% of girls and 83,6% of boys are with behavioral disorders and 9,6% of girls and 7,6% of boys have no behavioral disorders.

The impact of smoking on a child's body is a serious problem in pediatrics [17]. Studies by professor S.M. Gavalov (1988) showed that smoking leads to the development of chronic pathology of respiratory organs of adolescents[11]. Even a single cigarette causes functional changes in the lungs of adolescents, it particularly reduces the ability of lungs and chest to expansion [18].

At smoking in the respiratory tract various components of tobacco smoke penetrate: oxide and carbon dioxide, acrylic aldehyde, which act as household irritants. Tobacco smoke causes oxidative stress and stimulate inflammation in both the upper and lower respiratory tracts [14]. Regular nicotine intake primarily harms the respiratory system. First the adolescence experiences shortness of breath under minimal physical activity and then complains about a protracted dry cough and dyspnoea [15].

In Yakutsk over the past decade a study of the prevalence of tobacco use among adolescents had not been conducted.

Purpose: to study of the prevalence of

Table 1

Structure of the interviewed adolescents of Yakutsk by age and sex, n (%)

Group	n	13-14, n (%)	15-17, n (%)	p
Boys	533	220 (41,3)	313 (58,7)	0,922
Girls	398	163 (41)	235 (59)	
Both genders	931	383 (41,1)	548 (58,9)	

Note: p- stands for the achieved level of statistical significance of differences when comparing groups by age structure.

Table 2

Smoking experience of Yakutsk adolescents

Age group	In total	Boys	Girls	p
	n (%)	n (%)	n (%)	
13-14 y.o.	83 (21,7)	51 (23,2)	32 (19,6)	0,443
15-17 y.o.	303 (55,3)	160 (51,1)	143 (60,9)	0,023
13-17 y.o.	386 (41,5)	211 (39,6)	175 (44,0)	0,179

Note: p- the achieved level of statistical significance of differences when comparing girls and boys.

Table 3

Status in relation to smoking at the time of the survey

Smoking status	13-17 y.o.	13-14 y.o.	15-17 y.o.	p
	n (%)	n (%)	n (%)	
Boys N=533				
On a daily basis	17 (3,2)	2 (0,9)	15 (4,8)	<0,001
Occasionally	44 (8,3)	6 (2,7)	38 (12,1)	
Do not smoke at all	472 (88,5)	212 (96,4)	260 (83,1)	
Girls N=398				
On a daily basis	20 (5,0)	4 (2,5)	16 (6,8)	<0,001
Occasionally	45 (11,3)	8 (4,9)	37 (15,7)	
Do not smoke at all	333 (83,7)	151 (92,6)	182 (77,4)	

Note: p- the achieved level of statistical significance of differences when comparing age groups 13-14 and 15-17 years..

Table 4

Experience of daily smoking

Age group	In total	Boys	Girls	p
	n (%)	n (%)	n (%)	
13-14 y.o.	15 (3,9)	7 (3,2)	8 (4,9)	0,389
15-17 y.o.	107 (19,5)	51 (16,3)	56 (23,8)	0,028
13-17 y.o.	122 (13,1)	58 (10,9)	64 (16,1)	0,020
p*	<0,001	<0,001	<0,001	

Note: In the Tabl. 4-6 p- the reached level of statistical significance of differences when comparing groups by gender; p * - when comparing age groups 13-14 and 15-17.

Table 5

Share of children smoked 100 cigarettes

Age group	Both genders	Boys	Girls	p
	n (%)	n (%)	n (%)	
13-14 y.o.	12 (14,5)	5 (9,8)	7 (21,9)	0,128
15-17 y.o.	74 (24,4)	31 (19,4)	43 (30,1)	0,031
13-17 y.o.	86 (22,3)	36 (17,1)	50 (28,6)	0,007
p*	0,053	0,111	0,354	

Table 6

Number of cigarettes smoked by daily and occasional smokers

Age group	In total	Boys	Girls	p
	Me (Q1;Q3)	Me (Q1;Q3)	Me (Q1;Q3)	
Daily smokers				
13-14 y.o.	5,5 (1; 12,5)	15 (10; 20)	3 (1; 5,8)	0,060
15-17 y.o.	3 (3; 7)	3 (3; 5)	4 (3; 10)	0,383
13-17 y.o.	4 (3; 7)	4 (3; 7)	4 (3; 9)	0,963
p*	0,644	0,041	0,267	
Occasional smokers				
13-14 y.o.	2 (2; 3)	1 (0,75; 4)	3 (1; 3)	0,342
15-17 y.o.	3 (1; 4)	3 (1; 4,3)	3 (1; 4,5)	0,759
13-17 y.o.	3 (1; 4)	3 (1; 4)	3 (1; 4)	0,983
p*	0,232	0,213	0,779	

Table 7

Distribution of smokers by number of smoked cigarettes, n (%)

Smokers	Gender	Up to 5 cigarettes	5-10 cigarettes	10 cigarettes and more	p
daily	Boys	12 (70,6)	3 (17,6)	2 (11,8)	0,566
	Girls	13 (65,0)	6 (30,0)	1 (5,0)	
	Both genders	25 (67,6)	9 (24,3)	3 (8,1)	
occasional	Boys	36 (81,8)	7 (15,9)	1 (2,3)	0,587
	Girls	36 (81,8)	8 (18,2)	0 (0)	
	Both genders	72 (81,8)	15 (17,0)	1 (1,1)	

Note: p- the achieved level of statistical significance of differences when comparing gender groups.

smoking among adolescents in Yakutsk.

Materials and methods. The study was conducted on a representative sample of Yakutsk schoolchildren, for which six schools (№№14, 18, 27, 28, 31) had been selected from the list of all the general education institutions using a random number generator.

Students of grades 8-11 were invited to voluntary participation in the study. An anonymous survey involved 931 persons aged 13 to 17. The study used the questionnaire presented in the physician's guide edited by Prof. N.A. Geppe "Prevention of smoking among children and adolescents", designed to estimate the prevalence, causes and motivations of smoking among children and adolescents (2008).

Results and discussion

Age and gender structure of the respondents is presented in Table 1. Among the participants boys slightly outnumber girls (57.3% and 42.7%, respectively), but the age structure statistically did not significantly differ (p = 0.922).

According to the questionnaire, at the age of 13-17 386 (41,5%) of the schoolchildren had a smoking experience (Table 2). Among the middle school students (13-14 y.o.) 21,7% had an experience of smoking. Among boys of this age 23.2% had a smoking experience, among girls - 19,6% (p=0,443). 55.3% of 15-17-year-olds had similar experience (51% among boys and 60.9% among girls, p = 0.023). Thus, at the age 13-17 42% of children had a smoking experience. The share of children with smoking experience increased by 15-17 years in comparison with 13-14 aged children in 2,6 times (p <0,001).

As it can be seen from Table 3, at the time of the survey 3,2% of boys and 5% of girls stated that they smoked daily, 8.3 and 11,3% smoked occasionally, respectively. In the senior age group the share of smokers was statistically higher, both among boys and girls (p <0,001). The presented survey data is lower than the global survey rates (2009) in the Russian Federation where 15,8% of 15-18 y.o. adolescents smoked on a daily basis [3]. Among American girls and boys studying in grades 7-12, 11% of schoolboys were regular smokers [16]. According to Y.E. Mazur et al. in Krasnoyarsk «heavy smokers» were accounted for 12,6%, «occasional smokers» - 5,2% [12]. Among the adolescents of Zabaykalsky Krai, 39.9% were daily smokers [3].

Among the respondents of Yakutsk at the age of 13-17 13.1% are those who ever smoked daily (Table 4). What is more along with the age-specific pattern of the indicator, there has been a high frequency of daily smoking experience among girls aged 15-17 (p=0,028).

To the question "Have you smoked 100 cigarettes in your entire life?" 17% of boys and 29% of girls at the age of 13-17 gave a positive respond (p=0,007). The share of girls statistically was significantly higher in the 15-17 age group (Table 5). In the younger group, due to the small number of observations, the differences were not statistically significant.

When analyzing the number of cigarettes smoked per day it was noted that daily smoking children on average smoked 4 cigarettes per day, occasional smokers - 3 (Table 6).

According to scientists, regardless of number of cigarettes consumed per day, regularly smoking adolescents constitute a risk group who have serious health abnormalities by high school graduation [9].

Among daily smokers 71% of boys and 65% of girls smoked up to 5 cigarettes per day (Table 7). 18% of boys and 30% of girls smoked 5-10 cigarettes per day, 12 and 5% - more than 10 cigarettes, respectively. Among occasional smokers 18% of children smoked 5 or more cigarettes per day.

Conclusion. The study showed the widespread smoking among schoolchildren of Yakutsk. Prevalence of tobacco smoking was 41.5%, while girls smoke more often than boys, 44.0% and 39.6%, respectively. Every day 3.2% of boys and 5% of girls smoke, 8.3% of boys and 11.3% of girls smoke occasionally. Adolescents began to smoke regularly at the age of 13. The proportion of children with smoking experience by the age of 15-17 is 2.6 times higher than that of the group of children aged 13-14, which indicates the steady development of nicotine addiction in adolescents of this age.

Thus, tobacco smoking among adolescents is a social and medico psychological problem. It is during adolescence when cigarettes cause the most harm, along with climatic and ecological conditions serve as risk factors for formation of chronic bronchopulmonary diseases. To reduce the prevalence of smoking among children and adolescents, a competent, science-based program combining both preventive and special methods of rehabilitation is necessary.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

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MORBIDITY OF POPULATION IN THE CENTRAL ECONOMIC ZONE OF THE SAKHA (YAKUTIA) REPUBLIC

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ABSTRACT

The analysis of the incidence rate for the period 2007-2016 was carried out (in the age aspect - since 1992) in the Central Economic Zone of the Sakha (Yakutia) Republic, which included such regions / uluses as Amginsky, Gorny, Kobyaysky, Megino-Kangalassky, Namsky, Tattinsky, Ust-Aldansky, Khangalassky and Churapchinsky, and also the capital of the republic Yakutsk. According to medical and geographical zoning, these municipalities are part of a group of central and behind the river districts. At the same time, the general and primary morbidity of both the general population and the age range in adults and children (0-14 years) of the population was considered. According to the medical-demographic indicators and morbidity data, the most alarming situation is in Kobyai district, therefore, appropriate management decisions are needed from both the municipality and the Republic's Ministry of Health.

The analysis was carried by the percentile method, first as a whole in the Republic, then in the selected uluses. Thus, the incidence rate for these uluses is positioned in comparison with the indicators of all administrative-territorial entities of the Sakha (Yakutia) Republic.

Keywords: general morbidity, primary, adult morbidity, morbidity of children, Central Economic Zone, the Sakha (Yakutia) Republic.

Introduction. The indicator of the incidence of the population (general and primary, in the age aspect, according to the main classes of diseases, etc.) is one of the main criteria of public health. According to state or departmental statistics, the level of morbidity in one or another territory is determined. In the approved Strategy of socio-economic development of the Sakha (Yakutia) Republic until 2030, with the definition of the main directions until 2050, there are sections directly or indirectly affecting the health sector: demographic and family policy, innovative healthcare development, physical culture and sport, social protection of the population. In the section "Development of territorial planning" the entire territory of the republic is divided into 5 economic zones: Arctic, Western, Central, Eastern and Southern.

Since indicator values of the expected results are planned by 2030, there is a need to evaluate some or other characteristics of public health of the population at this stage, including morbidity. In this article, we will analyze the incidence in the Central Economic Zone (CEZ).

Material and methods of the research. In the article the materials of the official statistics of the Republic (Sakha (Yakutia) stat) and the Ministry of Health (YRMIAC) were used [1-3]. For the analysis of these statistical data, the percentile (centile) method used by us in developing the criteria for the regionalization of the North of the Russian Federation and for the preparation of a number of articles was used. According to this method, the areas with indicators up to the 10th percentile belonged to territories with a low incidence rate, from 10 to 25th percentile - with a level below the average, from 75 to 90 - above the average and over 90th per centile high level. Obviously, with the indices lying within the 25th to the 75th percentile, the regions belonged to a group with average morbidity rates.

The analysis was carried by the percentile method, first as a whole in the Republic, then in the selected uluses. Thus, the incidence rate for these uluses is positioned in comparison with the indicators of all administrative-territorial entities of the Sakha (Yakutia) Republic.

Results and discussion. The general and primary morbidity of the population of the Central economic zone in 2007-2016 is presented in Table 1. For the overall morbidity (morbidity), the best position is occupied by the Gorny and Khangalassi uluses - low-level periods were recorded for 4 years. After them there are the Megino-Kangalassky, Churapchinsky uluses

Table 1

The general and primary morbidity of the population of the CEZ RS (Ya) in 2007-2016. (per 1000 of population)

District	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
General morbidity										
Amginsky	2199,0	2272,2	2335,5	2666,3	2679,4	2851,8	2894,7	2566,1	2682,5	2302,9
Gorny	1648,9	1673,3	1829,8	1603,7	1515,6	1526,8	1602,6	1541,7	1659,3	1618,1
Kobyaysky	1891,0	1808,0	1969,8	1594,9	1841,0	2289,8	2476,2	2224,2	2474,1	2042,4
M-Kangalassky	1314,3	1315,3	1491,4	1688,9	1668,0	1834,1	2038,6	1960,4	2041,2	1816,2
Namsky	2399,8	2290,3	1974,4	1649,0	1669,2	1796,4	1892,3	1840,6	1819,9	1682,4
Tattinsky	1693,1	1658,5	1772,1	1936,7	1866,0	2044,5	2196,8	2085,0	1835,7	1818,7
Ust-Aldansky	1568,7	1524,3	1904,4	2065,4	2349,5	2341,8	2562,3	2341,4	1888,4	1881,7
Khangalassky	1276,8	1240,6	1350,2	1365,7	1501,2	1705,2	1819,1	1906,7	1931,7	1886,9
Churapchinsky	1717,6	1578,9	1821,2	1766,0	1694,2	1731,7	1752,1	1684,2	1717,5	1556,1
Yakutsk	1625,9	1671,6	1862,1	1852,5	1813,7	1697,6	1759,5	1742,2	1877,6	1806,7
In the RS (Ya)	1710,2	1759,2	1844,2	1858,7	1863,6	1930,3	2005,7	1973,7	2016,8	1919,2
Primary morbidity										
Amginsky	1332,2	1624,0	1618,5	1812,1	1818,4	1770,7	1804,6	1627,0	1528,6	1548,0
Gorny	901,2	869,7	1088,3	953,7	825,1	846,9	883,6	915,2	936,4	1151,6
Kobyaysky	1138,4	1071,7	1214,7	975,1	1095,8	1311,8	1476,9	1339,3	1391,8	1253,3
M-Kangalassky	717,6	715,6	825,2	946,8	908,1	937,0	1032,1	970,7	937,7	1021,1
Namsky	1348,6	1099,0	1028,0	850,3	820,9	889,3	1062,9	1049,9	836,0	931,7
Tattinsky	960,8	973,5	1059,4	1158,4	1117,8	1215,1	1344,6	1224,4	1063,4	1096,5
Ust-Aldansky	949,5	827,1	962,9	1131,6	1213,7	1144,6	1299,1	1253,8	642,0	1004,7
Khangalassky	717,7	695,1	708,3	786,5	880,5	1025,1	1069,8	1139,3	1090,3	1114,3
Churapchinsky	970,6	824,2	973,6	1031,7	1021,1	1041,7	1102,1	1024,0	1002,2	913,3
Yakutsk	829,4	947,3	1002,0	998,7	986,0	910,7	919,1	927,1	886,8	931,4
In the RS (Ya)	940,5	987,0	1014,8	1032,8	1046,0	1065,0	1106,4	1098,1	1026,6	1043,8

Note. In the Tabl. 1-3 legend:

3739,1	high morbidity	1416,5	level below average
3162,2	level above average	1158,3	low morbidity

and the city of Yakutsk - during this period, the average and below average morbidity levels are generally observed. Relatively high morbidity levels are observed in the Kobyaysky, Ust-Aldansky Ulus and, especially, in the Amginsky Ulus. Amginskiy Ulus "distinguished" by the fact that from 2007 to 2014 it had high levels of morbidity, although then the level decreased but still remained above mean value.

Primary morbidity was relatively high in the Amginsky and Kobyaysky ulus, with a high level in the Amginsky ulus for the entire period under review. In addition to average values, the level below the average and low was recorded in such regions as Megino-Kangalassky, Khangalassky, Churapchinsky, and also in Yakutsk.

The indicators of the general and primary morbidity of the adult population of the Central Economic Area for 1992, 1995, 2000, 2005 and the period 2010-2016 are presented in Table 2. It can be seen that in the Amginsky ulus, with the exception of 2005, then relatively high morbidity rates are observed. Also, not all is well for the overall morbidity in Ust-Aldansky (since 2005) and for the primary one in Kobyaysky.

The situation for the overall morbidity is better in Gorny (from 2012), Khangalassky (in 2005, 2010-2013) and Churapchinsky (from 2013) uluses. For primary morbidity, good indicators are observed in the Gorny (2012-2015), Megino-Kangalassky and Ust-Aldansky (before 2005) uluses and in Yakutsk (in 2000, 2013-2015).

As for children, the overall and primary morbidity of children in the CEZ is ambiguous: there are uluses with relatively high, and there are relatively low levels for 1992-2016 (Table 3). Thus, relatively high levels were registered in the Amginsky (from 2010) and Kobyay (in different years) ulus, relatively low - in Megino-Kangalassky (since 1995) and Ust-Aldansky (except for 2012 for the total incidence). Also good indicators for primary morbidity in the Gorny District, but here are the general years with an above average incidence rate (1992, 2005).

The conclusion. Thus, the situation of the overall and primary morbidity in 9 uluses / Districts and Yakutsk, representing the Central Economic Zone, is generally am-

Table 2

The general and primary morbidity of the adult population of the CEZ RS (Ya) in 1992, 1995, 2000, 2005, 2010-2016. (per 1000 adult population)

District	1992	1995	2000	2005	2010	2011	2012	2013	2014	2015	2016
General morbidity											
Amginsky	1022,6	1000,1	1485,7	977,2	2325,0	2362,8	2278,4	2292,5	2218,5	2331,4	1925,3
Gorny	1516,6	1320,8	1244,5	1429,1	1460,4	1459,5	1334,0	1386,7	1270,3	1369,1	1254,1
Kobyaysky	1332,5	1149,8	1072,5	1453,4	1278,3	1420,7	1811,2	2053,5	1758,2	2016,3	1563,8
M-Kangalassky	1166,6	970,8	1064,1	1147,5	1577,4	1612,3	1825,4	2084,8	1978,9	2057,4	1750,5
Namsky	1423,5	1258,2	1231,4	1401,6	1500,2	1569,5	1604,0	1617,0	1580,8	1614,6	1473,6
Tattinsky	1096,7	1052,7	1225,9	1547,1	1625,5	1746,9	1694,2	1758,5	1656,7	1493,4	1440,7
Ust-Aldansky	1034,6	820,5	816,4	1481,0	1696,2	1971,2	1751,4	2208,6	2183,7	1705,4	1735,2
Khangalassky	1226,1	1486,0	1148,5	1085,5	1074,3	1199,4	1386,2	1512,3	1496,1	1576,5	1446,8
Churapchinsky	842,7	696,6	985,5	1643,4	1566,9	1443,4	1397,6	1400,1	1419,7	1430,9	1307,6
Yakutsk	990,7	1053,9	1004,6	1323,1	1577,6	1599,9	1446,5	1510,2	1470,6	1599,2	1519,1
In the RS (Ya)	1167,8	1102,0	1098,3	1407,4	1590,4	1586,4	1647,0	1740,6	1708,6	1755,9	1635,8
Primary morbidity											
Amginsky	680,0	610,8	1011,5	464,6	1269,7	1208,6	1007,9	994,6	966,2	938,4	937,2
Gorny	756,9	735,3	642,6	631,9	661,5	594,4	537,9	535,5	530,3	491,3	626,9
Kobyaysky	881,9	684,9	505,9	705,3	562,0	577,5	759,0	991,5	763,7	790,8	588,2
M-Kangalassky	549,3	472,9	373,4	439,8	549,5	662,2	685,1	779,7	684,3	632,8	733,3
Namsky	924,1	693,9	665,8	779,3	559,6	557,5	552,7	603,2	586,1	464,2	626,5
Tattinsky	635,8	571,2	611,7	651,6	691,3	712,0	683,5	699,4	576,1	535,1	630,0
Ust-Aldansky	551,1	385,9	341,1	521,2	609,9	672,1	567,3	764,9	792,1	551,8	628,1
Khangalassky	636,3	681,0	520,8	474,8	447,3	493,4	600,5	611,6	590,3	589,9	539,2
Churapchinsky	543,0	356,6	535,9	703,9	634,1	608,5	554,5	612,8	579,5	534,2	469,0
Yakutsk	599,1	565,9	422,0	539,8	624,2	634,8	554,9	557,8	554,5	515,5	519,6
In the RS (Ya)	693,4	617,4	527,6	634,9	652,0	649,3	650,6	689,9	671,8	619,0	610,6

Table 3

The general and primary morbidity of the children of the CEZ RS (Ya) in 1992, 1995, 2000, 2005, 2010-2016. (per 1000 child population 0-14 years)

District	1992	1995	2000	2005	2010	2011	2012	2013	2014	2015	2016
General morbidity											
Amginsky	1543,9	1564,1	1544,3	1318,1	3358,8	3994,5	4069,6	4146,8	3319,7	3435,8	3152,2
Gorny	1930,0	1306,1	1465,3	2385,8	2039,1	1973,9	1963,7	2099,0	2101,5	2217,9	2396,2
Kobyaysky	2085,5	1764,7	1605,7	2310,7	2432,5	3076,6	3417,2	3443,4	3314,4	3502,0	3157,5
M-Kangalassky	1703,8	1254,4	1207,1	1381,0	1910,0	1807,0	1781,6	1885,6	1896,2	1916,1	1953,0
Namsky	2989,3	2295,2	1779,6	1866,8	1972,4	2076,7	2138,6	2536,1	2380,2	2249,8	2099,2
Tattinsky	1361,3	1569,4	1678,2	1809,6	2672,8	2861,6	2853,2	3249,7	3100,3	2595,2	2702,2
Ust-Aldansky	1564,4	1082,8	1167,0	1648,5	2985,9	3672,5	3278,8	3293,8	2621,0	2281,5	2162,0
Khangalassky	1671,7	1483,4	1470,5	1579,0	2251,1	2415,3	2660,4	2787,8	3148,3	3001,2	3202,3
Churapchinsky	1024,2	1089,8	1618,0	2449,7	2193,4	2267,1	2355,8	2491,0	2272,4	2309,9	2039,2
Yakutsk	1555,9	1838,4	1800,6	2349,5	2903,3	2934,4	2686,0	2720,4	2748,1	2862,7	2941,8
In the RS (Ya)	1601,9	1600,2	1658,3	2113,0	2736,1	2761,1	2828,9	2855,9	2779,1	2773,3	2774,5
Primary morbidity											
Amginsky	1343,6	1387,6	1369,1	1107,1	2886,2	3501,4	3451,3	3533,8	3037,9	2790,7	2876,0
Gorny	1382,6	968,2	1099,9	1579,4	1716,7	1546,2	1562,4	1692,3	1762,7	1837,1	2247,6
Kobyaysky	1849,3	1478,6	1349,2	1899,2	2086,6	1985,4	2668,8	2676,3	2684,7	2794,6	2870,6
M-Kangalassky	1102,4	918,0	911,1	874,3	1632,0	1470,4	1441,4	1569,2	1575,1	1509,6	1620,8
Namsky	2425,6	1845,3	1389,6	1179,5	1509,0	1487,5	1663,5	2143,2	2090,2	1645,0	1833,3
Tattinsky	1043,2	1299,7	1379,9	1226,5	2225,5	2479,3	2468,0	2889,4	2767,6	2277,5	2348,5
Ust-Aldansky	1286,2	870,6	869,2	1070,3	2348,1	2666,5	2248,2	2369,9	2200,1	806,5	1824,7
Khangalassky	1364,0	1194,1	1052,4	1185,2	1794,0	2029,4	2344,5	2515,1	2812,9	2616,0	2832,4
Churapchinsky	900,2	929,3	1344,5	2061,3	1850,4	1907,8	2038,5	2163,8	1985,4	1996,5	1818,0
Yakutsk	1423,2	1458,1	1375,8	1794,9	2385,0	2459,5	2260,3	2252,0	2261,4	2169,5	2449,0
In the RS (Ya)	1317,4	1330,7	1324,5	1612,4	2255,0	2312,0	2373,9	2410,0	2374,9	2218,5	2338,4

biguous. Relatively high levels of these indicators were noted during the period under review in the Amginsky and Kobyaysky uluses, relatively low in the Gorny, Megino-Kangalassky, Khangalassky and Churapchinsky uluses (although with single indicators that characterize the above-average incidence rates).

In Namsky and Tattinsky Ulus, mean values are generally noted, although there are years with different levels of general and primary incidence. The situation in the Ust-Aldansky ulus is favorable for children's morbidity, and in Yakutsk - for the incidence of the adult and the entire population.

Since we previously analyzed the medical and demographic situation in 8 uluses / districts and the city of Yakutsk, representing the Central Economic Zone (Yakutsk Medical Journal, No. 1 (61) for 2018), it is possible to assess the health status of the population in these territories by medical demographic indicators and incidence data. The most alarming situation is in Kobyajskiy district, in connection with which, in our opinion, appropriate management decisions are necessary both from the municipality and the Ministry of Health of the Republic.

The work was prepared based on the results of the project "Assessment, the main trends in the natural and socio-economic condition, human potential of the Central Economic Zone of the Sakha (Yakutia) Republic" of the Integrated Scientific Research Program in the Sakha (Yakutia) Republic aimed at developing its productive forces and social sphere in 2016-2020 years.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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THE ROLE OF EXPEDITIONARY RESEARCH IN STUDYING THE HEALTH OF THE POPULATION OF VILYUI REGION

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ABSTRACT

In order to preserve the original habitat, culture and traditional way of life, the health of the population of the North is of fundamental importance. The first public health studies at the state level were carried out by members of the medical and sanitary unit as part of the first complex Yakutsk expedition of the USSR Academy of Sciences (1925-1928). Subsequently, the ideas and forms of work of the Yakut expedition of the Academy of Sciences of the USSR continued to be realized by their followers. In the 60-90s of the twentieth century, a study began of the state of health of the population of the republic, including the Vilyuysk group of uluses, which turned out to be on the territory of industrial pollution by enterprises of the diamond-mining industry and the Vilyuiskaya hydroelectric station. The knowledge obtained during long-term monitoring studies makes it possible to make a long-term forecast of possible environmental changes under conditions of climate change and anthropogenic impact. The Vilyui group of uluses was characterized by transgressive water migration enriched with microelements, petroleum products and phenol. This is associated with the accumulation of toxic elements, industrial poisons in the river fauna, in fish tissues, in humans and animals. Proof of this are the established high concentrations of micro and macronutrients in the hair and in the blood of the representatives of the indigenous population. The obtained results can be used in planning programs for the socio-economic development of the Vilyui region of the Sakha Republic (Yakutia) and individual administrative regions and municipalities of the republic, in the development of projects for the integrated development of mineral deposits, the use of agricultural land, and environmental protection measures. Research materials should be used by the supervisory authorities to monitor the state of public health and the environment. In August 2018, as a result of the destruction of the dams of the dredging pits of the Irelyakhskaya placer mine of the Mirny mine, Alrosa company, pollutants were released to the Irelya, Malaya Botuobuya and Viluy rivers. Huge damage has been inflicted on water bodies, aquatic biological resources and the population living in this region. Currently, environmentalists are working, but the medical community also needs to be connected, because the pollution of water bodies, given the slow recovery typical of northern ecosystems, will inevitably affect the health of the population.

Keywords: nature, ecology, health, monitoring, technogenic influence, anthropogenic influence, ecosystems, development programs, regions.

Back in the XIX century, the works of individual naturalists found that the natives of the North (Eskimos, Nenets, Chukchi, evens, Yakuts, etc.) have their morphological and physiological characteristics that ensure their adaptation to the conditions of existence, formed under the influence of biological and social factors of the environment. Difficult

living conditions in extreme natural and climatic conditions affected human health and quality of life, especially great problems related to the health of children (low survival of newborns, high mortality). For example, the General population census of 1897 proved the hypothesis of the extinction of the Yakut people (population growth for 20 years was only 1.5 thousand people) [1, 2].

After the establishment of Soviet power in Yakutia, special attention was paid to the health of the indigenous population. In his address to the Academy of Sciences of the USSR, The young leader of the Yakut people M. K. Ammosov wrote: "the October revolution created a political prerequisite for backward Yakutia, and the expedition of the Academy of Sciences should provide the scientific basis for this revival" [3].

The first studies of public health at the state level were conducted by employees of the medical and sanitary unit under The leadership of S. E. Schreiber as part of the I complex Yakut expedition of the USSR Academy of Sciences (1925-1928). The squad worked in Yakutsk, and Viliuisk, Olekminsk districts and, separately, in the Viluy leper colony [4].

The results of the surveys were disappointing: among children and women there was a continuous disease of tuberculosis, infant mortality was above 50%. Doctors have identified a number of social diseases. Thus, trachoma, which covered up to 45% of the total population, led to the fact that about 3.5% became completely blind and half-blind [5]. Epidemics of smallpox, scarlet fever and measles were rampant. Among the local population there was a high prevalence of intestinal diseases caused by poor and irrational nutrition [6].

As the main cause of morbidity, the medical and sanitary team noted the poor sanitary condition of life, poor nutrition, prevalence of smoking and alcohol consumption, the lack of real medical care [6].

Subsequently, the ideas and forms of work of the Yakut expedition of the Academy of Sciences of the USSR continued to be realized by their followers. So, by the institutes of SB RAMS, medical faculty of YSU, Academy of Sciences of RS (Ya) in 60-90-ies of XX century began the study of the health of the population of the Republic, including Vilyui group, caught in the territory of industrial pollution enterprises of the diamond industry and Vilyui HPP [7, 8].

The results and discussion. Vilyu regions enterprises of the diamond mining industry are one of the first industrial complexes of Yakutia and are located on the Vilyui river. In the formation of the Vilyui hydroelectric power station reservoir were flooded coniferous forests area of 2335 km2 and, as mentioned in "Memorandum" of the Commission of the USSR Academy of Sciences, from 19-25 August 1983, water quality in the reservoir in the first 2-3 years after filling was dramatically unsatisfactory. Thus, the concentration of phenols reached 30-40 MPC, there were large areas of hydrogen sulfide contamination. The note also stated that "there was a sharp deterioration in water quality throughout the Viluy river." In many settlements along the river, there was an increased incidence of acute intestinal infections, infectious hepatitis, pathology of pregnancy and childbirth, etc. [9, 10].

Iron oxides, aluminum, chromium, titanium and other elements, which were passed through the mouth of the river Irelyakh in the basin of the river Vilyuy in the composition of highly mineralized waters. About the anthropogenic character of changes in the composition of the Vilyui river in those years is evidenced by the analysis of the data of hydrometeorological service of the Republic of Sakha [11].

The role of shifts in the content of trace elements in the development of diseases is indirectly confirmed by the accumulation of aquatic phytophlora and river living organisms of trace elements such as Nickel (4-7 times) chromium, lead, iron (up to 7 or more times), copper and zinc (2 times), and aluminum and manganese up to 20 times. In Daldyn river vitaflora additionally accumulates silver, cobalt, compared with fitotehnie intact creeks flowing into the river basin. It is important to note that the concentration of Nickel, chromium, titanium, boron and silver in the hair is the highest in children. This can be explained by the affinity of trace elements to the tissues of a growing organism [12, 13].

At the end of the XX and the beginning of the XXI century began to study the relationship of pathological changes in the human body with the trace element composition of the environment and the role of trace elements in the development of diseases.

We studied the content of chemical elements in the hair of adults and children of Vilyui region. Our results indicate frequent contacts of men with elements-toxicants (professional contacts, contamination of the environment), which is consistent with the data by D. D. Savvinov and N. N. Sazonov studied their content in the environment [11].

During these years the mill tailings was found to have a high content of iron oxides, aluminum, chromium, titanium and other elements, which were passed through the mouth of the river Irelyakh in the basin of the river Vilyuy in children living in the Viliuisk region, also observed the imbalance in the content of some chemical elements, particularly in relation to the contents of Be, Sn, Ca and Se boys got into a more "scarce" group than in the other regions.

Girls have a relatively high content of Cr and Si in their hair and a low content of Ca and Mg. In connection with the established facts, it is now extremely important to study the resistance of the body to monitor the health of the local population.

Therefore, one of the stages of the work was the study took the state of the environment (water, soil, bottom sediments) and its impact on the health of the inhabitants of the Vilyui region.

The relationship of the prevalence of certain diseases with the elemental composition of the hair is established. So, the residents of the Vilyui zone due to excessive accumulation in the hair Cr, Fe, K, Mn, Va, Pb and Si and the relatively low content of Ca, Co, I, Mg, Se and Zn have higher morbidity according to classes X, IX, III, IV, VI and XIX, and the children – I, IV, II, VI, XIII and XII.

Thus, we can conclude that the Vilyui group was characterized by water transgressive migration, fortified foods, oil products and phenol. This is due to the accumulation of toxic elements, industrial poisons in the river fauna, in the tissues of fish, in humans and animals. The established high concentrations of micro - and macronutrients in the hair and blood of indigenous people, as well as highly toxic poison-boron, in the hair of children with apilation serve as proof of this [13, 14].

In the first years of the XXI century the budget financing of many scientific researches has sharply decreased and expedition works have practically stopped. During these years, work continued only

Table 1

The incidence of infectious hepatitis per 100,000 population in the uluses of the Vilyui region of the Republic of Sakha (Yakutia)

uluses	1988	1989	1990	1991	1992	1993	1994
Vilyuisk	314,1	455,5	169,9	162,1	454,9	717,9	1007,0
Verkhnevilyuysky	775,4	343,9	218,0	211,3	641,5	1050,7	1811,1
Nyurbinsk	311,8	388,4	193,8	406,8	2681,2	2063,5	441,1
Suntarsky	681,4	397,4	372,2	500,0	1245,4	1619,9	1198,5
Republic RS (Y)	279,5	241,2	341,3	370,1	380,0	350,3	303,9

Table 2

The dynamics of the main epidemiological indicators of tuberculosis in the uluses of the Vilyui region of the Republic of Sakha (Yakutia) per 1000 population

uluses	Morbidity			Incidence			Bacillary			Mortality		
	1980	1992	1994	1980	1992	1994	1980	1992	1994	1980	1992	1994
Vilyuisk	780,6	381,0	442,8	75,9	71,4	84,8	305,3	119,0	136,4	9,3	6,8	3,7
Verkhnevilyuysky	890,1	300,0	442,1	148,3	88,8	86,0	322,0	214,9	196,5	11,4	9,8	11,1
Nyurbinsk	602,7	395,3	568,6	99,2	94,6	277,1	277,1	141,9	273,2	10,0	6,8	9,2
Suntarsky	814,1	353,4	242,0	146,0	318,8	301,7	301,7	102,7	66,4	9,6	7,1	7,0
Republic RS (Y)	448,2	252,5	240,3	71,9	48,6	55,9	180,2	86,5	79,9	8,6	7,4	6,9

Table 3

Complications, course and outcomes of pregnancies in the uluses of the Vilyui region of the Republic of Sakha (Yakutia) for 1982-1992 (per 1000 pregnant women)

uluses	1983	1985	1990	1991	1992
Vilyuisk	427,1	439,9	817,6	801,3	1036,2
Verkhnevilyuysky	397,3	318,7	253,8	495,8	675,8
Nyurbinsk	396,3	472,2	336,2	483,1	678,5
Suntarsky	198,0	359,8	595,4	677,0	607,6
	397,4	205,6	207,0	315,6	355,9
Republic RS (Y)	309,7	359,7	450,6	611,1	515,2

Table 4

Complications of childbirth in women in labor of uluses of the Vilyui region of the Republic of Sakha (Yakutia) for 1983-1992 (per 1000 births)

uluses	1983	1985	1990	1991	1992
Vilyuisk	412,4	362,7	449,5	459,6	411,6
Verkhnevilyuysky	388,2	485,7	360,7	559,6	776,4
Nyurbinsk	329,5	246,8	579,0	723,7	543,9
Suntarsky	414,3	447,2	765,8	934,8	843,1
	330,7	380,5	321,5	618,2	513,3
Republic RS (Y)	273,9	329,4	444,7	641,5	695,3

in the Nyurba ulus on the initiative of the head of V. A. Petrova, concerned about the impact of the launch of the Nakyn diamond Deposit on the health of the population. Medical Institute together with the staff of the Institute of ecology of the North, Academy of Sciences of Sakha (Yakutia) held 5 scientific expeditions with the survey 5381 adults and 5415 children and adolescents in 18 towns and the city of Nyurba. The results of these comprehensive studies formed the basis of the collective monograph “habitat and human health in the North: ecological and medical aspects”.

The main results of scientific works in 1999-2002 in Nyurbinsky ulus stated the following: the general level of morbidity of children and adults above the average national indicators; the dependence of the level of morbidity of the population in certain forms of pathology on the state of the source of water supply and the degree of their pollution (r. Markha, r. Vilyui); trace element analysis in the hair of children showed increased concentrations of manganese, lead, associated with increased content of these elements in the soil, drinking water, bottom sediments.

The conducted immuno-epidemiological studies confirmed the high prevalence of chronic diseases as clinical “masks” of immunodeficiency States associated with the immune phenotype of the inhabitants of the North.

These results caused a certain public response and became one of the prerequisites for the implementation of programs for the prevention of the consequences of environmental pollution, protection of public health and the supply of clean drinking water.

Subsequently, on the initiative of the new head of the Nyurba V. M. Prokopiev in 2008, to continue monitoring the health of the population, medical Institute staff also went to work in 5 settlements. However, with the termination of further funding, monitoring of the health of other settlements did not work.

Table 5

The average content of chemical elements in the hair of adults in the Vilyui zone of Yakutia (μg / g)

Element	Women n=120	Men n=90
Al	14,2±2,05	17,27±2,8
As	0,1±0,056	0,11±0,013
B	0,98±0,17	1,23±0,36
Be	0,01±0,001	0,01±0,001
Ca	853±108	399±30
Cd	0,06±0,01	0,11±0,02
Co	0,04±0,01	0,03±0,01
Cr	0,53±0,04	0,72±0,04
Cu	10,94±0,25	10,5±0,26
Fe	21±2,37	23,45±1,93
Hg	0,74±0,08	0,74±0,08
I	1,3±0,18	1,22±0,6
K	543±102	825±108
Li	0,05±0,01	0,08±0,02
Mg	155±23	56±6
Mn	1,8±0,27	1,46±0,17
Na	847±150	875±128
Ni	0,38±0,05	0,31±0,05
P	168±6	186±13
Pb	1,45±0,22	3±0,43
Se	0,49±0,09	0,45±0,03
Si	48±7,31	32,15±2,7
Sn	0,25±0,05	0,2±0,05
V	0,07±0,01	0,08±0,01
Zn	167±5	161±4

Note: the content of microelements exceeding or below the reference values is highlighted (according to P. Bertram, 1992; with additions A.V. Skalniy, 2000).

Table 6

The average content of chemical elements in the hair of children from the Vilyui zone of Yakutia (μg / g)

Element	Girls n=175	Boys n=152
Al	14,35±0,7	15,09±1,08
As	0,08±0,004	0,14±0,013
B	1,69±1,26	1,34±0,5
Be	0,003±0,001	0,001±0,0002
Ca	313±13	246±9
Cd	0,11±0,01	0,15±0,01
Co	0,02±0	0,02±0
Cr	0,63±0,002	0,9±0,05
Cu	10,45±0,31	11,03±10,35
Fe	28,96±1,24	30,33
Hg	0,74±0,08	0,74±0,08
I	1,3±0,18	1,22±0,6
K	543±102	825±108
Li	0,05±0,01	0,08±0,02
Mg	155±23	56±6
Mn	1,8±0,27	1,46±0,17
Na	847±150	875±128
Ni	0,38±0,05	0,31±0,05
P	168±6	186±13
Pb	1,45±0,22	3±0,43
Se	0,49±0,09	0,45±0,03
Si	48±7,31	32,15±2,7
Sn	0,25±0,05	0,2±0,05
V	0,07±0,01	0,08±0,01
Zn	167±5	161±4

Note: the content of microelements exceeding or below the reference values is highlighted (according to P. Bertram, 1992; with additions A.V. Skalniy, 2000).

In 2013 on the initiative of the next head B. N. Popov implemented a project that also established a high prevalence of chronic diseases among the population and identified the main modifying risk factors for coronary heart disease such as hypertension, age factor, male gender,

Table 7

The relationship between individual classes of disease and the content of microelements in the hair of the population of the Vilyui zone of the Republic of Sakha (Yakutia)

Element	Class of diseases	
Gaps / imbalances Cr, Fe, K, Mn, Pb, Si	X. Respiratory system IX. Circulatory system III. Blood systems IV. Endocrine system VI. Nervous system XIX. Injuries and poisoning	I. Infectious diseases IV.Endocrine system II. Neoplasm XI. Digestive organs VI. Nervous system XIII. Bone Muscular System XVII. Congenital anomalies
deficienciesCa, I, Co, Mg, Se, Zn		

burdened heredity, obesity, hyperlipidemia and smoking.

At present, the new head A. M. Innokentyev is set to continue monitoring the health of settlements located in the Markha river basin. We believe that the continuation of expeditionary research will reveal and confirm the role of chronic environmental pollution (soil, water) by toxicants of the diamond industry on human health and the profile of widely encountered nosologies.

Regarding the monitoring of the health of the population of other areas of the diamond region, we can say that in accordance with the priorities of the Strategy of socio – economic development of the Republic of Sakha (Yakutia) until 2030 and determining the main directions until 2050, approved by the government of the RS(Ya), the Government of the Republic is implementing a program of integrated research in the RS (Ya). Under this program, the medical Institute of NEFU at the stage of 2016-2017 worked on the territory of the Verkhnevilyuysky ulus under the state contract: "Multifactorial study of the health status of the indigenous and alien population of the RS(Ya) in order to optimize regional programs to improve the quality of life of the inhabitants of the Republic, taking into account territorial and ethnic characteristics in the conditions of modern socio – economic development."

It should be noted that although the human genetic program provides the broadest opportunities for its implementation in a particular environment, however, limited energy and structural reserves of the body impose a fairly rigid framework on the possibility of its adaptation. The trend of changes in physiological functions also makes it possible to predict pre - and pathological changes in the body, observed in living in this ecological region, as well as to judge the patterns of formation of adaptive defense mechanisms in the process of life.

Conclusion. The results obtained in the course of many years of expeditionary research in the Vilyui region indicate that the price of adaptation in the studied conditions can become so high that it will cause not only a decrease in professional opportunities, but also the ability to produce healthy offspring.

In 2018-2019, it is anticipated that this project will be a comprehensive research with the transfer to the government of the Republic of Sakha (Yakutia) developed recommendations and technologies aimed at optimizing regional programmes to improve the quality of medical care and increase the longevity of human life in the North.

In August 2018, as a result of the destruction of the dams of the dredge pits of the Irelyakhskaya Deposit, the Mirninsky GOK of ALROSA, there was a release of pollutants in the rivers Irelyakh, Malaya Botuobuya and Vilyui. Huge damage has been caused to water bodies, water biological resources and the population living in the region. Currently, the work of environmentalists is underway, but it is necessary to connect the medical community, because the pollution of water bodies, given the slow recovery characteristic of the Northern ecosystems, will inevitably affect the health of the population.

In modern conditions, humanity can no longer develop further without environmental orientation in all spheres of life – from the economy to public consciousness and culture. That is why only on the basis of multifactorial becomes possible to develop scientifically-based approaches to the assessment and prediction of health.

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ECOLOGICAL AND TOXICOLOGICAL FACTORS CONTRIBUTING TO THE PREVALENCE OF POTENTIALLY HARMFUL TO HUMAN HEALTH BIOHELMINTHOSES OF FISH OF YAKUTIA

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ABSTRACT

During the study period on the Lena River, there is a slight increase in the prevalence of the pike with plerocercoids of *Diphyllobothrium latum*. The prevalence of the pike aged 4, 5, 6 years old is equal to 28.5, 33.3, and 36.3%, the infection intensity is from 1 to 5 specimens, the abundance index is 0.64, 0.55 and 1.09 specimens respectively. The infection of the pike aged 7, 9, 10 years old is 62.5, 60.0, 100%, with the infection intensity 1-8 specimens, the abundance index is 2.0, 3.4 and 4.25 specimens respectively. The total infection of the pike with plerocercoids of diphyllobothriasis is 45.0%, the abundance index is 1.4 specimens. For the period the infection of the burbot with the plerocercoids of *Diphyllobothrium latum*, the total prevalence was 66.6%, with the infection intensity from 2 to 11 specimens. Thus, the infection of 5-6-7-year-old burbots is 25.0, 37.5 and 71.4%, with the infection intensity 2-9 specimens, with the abundance index 3.71 specimens. The infection of the older age groups 8-9-10-11 year olds is 100%, the infection intensity is 4-12 specimens, the abundance index reaches up to 10 specimens.

The total infection of theburbot in the Viliuy river with *Triaenophorus nodulosus* plerocercoids is 36.8%. The prevalence of the burbotaged 4-5-6-7 years old is 16.6, 25.0, 44.4 and 36.3%, respectively, the infection intensity is from 1 to 3 specimens, the abundance index reaches 2.0 specimens. For the period the total infestation of the burbot aged 3-4-5-6-7 years old in the Lena river with *Triaenophorus nodulosus* plerocercoids is equal to 16.6, 25.0, 44.4, 36.3, 37.5% respectively, with the infection intensity 1-3 specimens, with the abundance index up to 0.75 specimens. In the burbot aged 9 years old the infection with *Triaenophorus nodulosus* plerocercoids is 100%, with the infection intensity 1 to 3 specimens, and the abundance index is more than 2 specimens. The total infestation of the burbot with triaenophorid larvae along the Lena River is 36.7%, and the abundance index is 0.67 specimens.

These studies broaden the understanding of the adaptive capabilities of various fish parasites when inhabiting a polluted environment and contribute to the further development of environmental toxicology and parasitology.

Keywords: parasite fauna, parasites, middle course of the Lena river, aquatic ecosystems, fish, pike, burbot, pollution, anthropogenic impact, cestodes.

Introduction. The problem of the infection with biohelminthiasis, among which the most common is diphyllobothriasis is of particular relevance for the Republic of Sakha (Yakutia). The infection with diphyllobothriasis was registered in 29 regions of the Republic and the city of Yakutsk. Despite the moderate trend of its decline, which has been observed since 2009, the infection rate in the Republic remains one of the highest in the Russian Federation. The average long-term incidence of diphyllobothriasis in the Republic was 188.9 per 100 thousand people, exceeding the average figure for the Russian Federation up to 30 times. At the same time, in a number of regions of the Republic the infection rates consistently exceed the average in the Republic: the Verkhnevilyuysky region (191.2 per 100 thousand people), Yakutsk (242.5), the Verkhnekolymsky region (277.4), the Namsky region (285.1), the Srednekolymsky region (322.8), the Bulunsky region (418.9), the Khangalassky region (531.7), the Olekminsky region (627.6), the Kobyaysky region (1167.2), the Zhigansky region (1415.8). Over the past 5 years, the infection has sharply increased in the Mirny region from 64.1 in 2010 to 369.1 in 2014 [3].

The current ecological state of the Lena river basin, associated with increasing anthropogenic impact, requires evaluation and forecasting of the changes occurring there. The need for such research is associated with the enormous importance of the Lena basin, primarily as a fishery and transport reservoir. In this respect, the left tributary of the Lena river – the Viliuy river, where the intensive mining is being conducted, is a convenient model for considering the anthropogenic impact on the ecosystem under present conditions. For this purpose, we have studied and compared the composition and structure of the parasite fauna of the pike and the dace of the middle course of the Lena river and the middle course of the Viliuy river.

The greatest anthropogenic load is experienced by the Lena river, especially by its large tributaries: the Aldan and Viliuy rivers. Such distribution of water use is due to a large number of industrial mining enterprises, fuel and power complex facilities and large settlements in the basins of these rivers.

Fish parasites are reliable indicators of the ecological state of the reservoir. Under intense man-made load the ecological stability of the system weakens, the fish immunity decreases, they become more susceptible to infectious and invasive diseases, and the indices of infestation of hosts by parasites are increased [11]. Parasites that develop with the participation of planktonic crustaceans are indicators of the increased level of biogenic elements dissolved in water. Domestic sewage pollution promotes the spread of a dangerous zooanthroponosis - *Diphyllobothrium latum* in lakes. Accordingly, this species will be an indicator in determining the level of contamination of the reservoir. *Ligula*

intestinalis infestation is a very reliable indicator in assessing the trophic status of the reservoir [4]. This is most clearly reflected in the fish of the Vilyui reservoir, where in recent years, as a result of the eutrophication of the reservoir and the replacement of the rheophilic forms of zooplankton with limnophilic on es, the contamination of the dacer by the harpians has increased [1].

The advantage of parasites over other test objects is that parasites, especially those with a complex development cycle, accumulate changes that occur in all parts of the trophic chains of the aquatic ecosystem, as well as fish parasites have a relatively short lifespan and therefore show the ecological state of the reservoir at present [9]. Consequently, parasites of fish serve as a reliable ecological indicator of the processes of eutrophication and dystrophy [4].

The aim of the study is to study the fauna of main species of fish cestodes, to ascertain characteristics of infection under changing ecological and toxicological conditions of the middle course of the Lena river and its tributaries.

Materials and methods of research. Fish helminthological dissection was carried out according to the method developed by K.I. Skryabin (1928) and modified with respect to fish by VA. Doghel and E.M. Leyman, and also in accordance with the Methodological instructive regulations 3.2.988-00 *Methods of sanitary-parasitological examination of fish, shellfish, crustaceans, amphibians, reptiles and products of their processing* [2]. We have examined 160 fish specimens of 2 species, including 51 pikes, 109 burbots.

The species of parasites found in fish has been determined according to *Manual of freshwater fish parasites of the USSR fauna* [6, 7, 8].

For the study, the regions with different anthropogenic load were selected: the middle course of the Lena river and its left tributary - the Viliuy river.

Results and discussion. To identify the environmental consequences of human impact on natural water bodies, the studies of the population biology of fish parasites are of particular value. The research of the specificity of occurrence and distribution of the number of cestodes that have a complex development cycle allows us to consider main ways of parasites adaptation to changing environmental conditions and hosts resistance to infection. *Diphyllobotrium* and *Triaenophorus* cestodes can be one of the objects for studying the population biology of parasites.

Diphyllobotrium and *Triaenophorus* cestodes are widely distributed parasites of the Holarctic fish. Three *Diphyllobotrium* species - *D. latum, D. dendriticum, D. ditremum* and two species *Triaenophorus* - *T. nodulosus* and *T. crassus* inhabit the freshwater bodies of the north-east of Asia. The cycle of *Diphyllobotrium* development has two intermediate hosts. The first intermediate host is the planktonic copepods of *Copepoda* - 7 species. The composition of the second intermediate host *D. latum* in the conditions of Yakutia includes 5 fish species, *D. dendriticum* - 2 species, *D. ditremum* - 4 species [10]. The main final hosts are carnivores and humans.

The cycle of *Triaenophorus* development has two intermediate hosts. The first intermediate host for both *Triaenophorus nodulosus* and *Triaenophorus crassus* is the planktonic copepods of Copepoda. The composition of the second intermediate host of both species includes 6 species (taimen, grayling, pike, ruff, burbot, perch, dace, roach) for *Triaenophorus nodulosus*, whitefish species for *Triaenophorus crassus*. The main final host for both species is the pike *Esoxlucius L.*, in the intestine of which parasites reach sexual maturity [11].

Like helminthes with a complex development cycle, these species of cestodes of *Diphyllobotrium* and *Triaenophorus* give great information about the composition and abundance of the fish population and zooplankton in the reservoir. The infection of potential hosts with *Diphyllobotrium* and *Triaenophorus* cestodes also allows to determine the anthropogenic impact of the pollutants on the hydrobionts of freshwater reservoirs.

For the period of 2011-2015 there is a slight increase in the prevalence of the pike with plerocercoids of Diphyllobothrium latum. The prevalence of the pike aged 4, 5, 6 years old is equal to 28.5, 33.3, and 36.3%, the infection intensity is from 1 to 5 specimens, the abundance index is 0.64, 0.55 and 1.09 specimens respectively. The infection of the pike aged 7, 9, 10 years old is 62.5, 60.0, 100%, with the infection intensity 1-8 specimens, the abundance index is 2.0, 3.4 and 4.25 specimens respectively. The total infection of the pike with plerocercoids of diphyllobothriasis is 45.0%, the abundance index is 1.4 specimens (Table 1).

For the period of 2011-2015 the infection of the burbot with the plerocercoids of *Diphyllobothrium latum*, the total prevalence was 66.6%, with the infection intensity from 2 to 11 specimens. Thus, the infection of 5-6-7-year-old burbots is 25.0, 37.5 and 71.4%, with the infection intensity 2-9 specimens, with the abundance index 3.71 specimens. The infection of the older age groups 8-9-10-11 year olds is 100%, the infection intensity is 4-12 specimens, the abundance index reaches up to 10 specimens. (Table 2).

The influence of the size-age composition of the burbot on its infection with *Triaenophorus nodulosus* plerocercoids.

The total infection of the burbot in the Viliuy river with *Triaenophorus nodulosus* plerocercoids is 36.8%. The prevalence of the burbot aged 4-5-6-7 years old is 16.6, 25.0, 44.4 and 36.3%, respectively, the infection intensity is from 1 to 3 specimens, the abundance index reaches 2.0 specimens. (Table 3).

For the period of 2011-2015 the total infestation of the burbot aged 3-4-5-6-7 years old in the Lena river with *Triaenophorus nodulosus* plerocercoids is equal to 16.6, 25.0, 44.4, 36.3, 37.5% respectively, with the infection intensity 1-3 specimens, with the abundance

Table 1

Distribution of *Diphyllobothrium latum* plerocercoids in the pike along the middle course of the Lena river (2011-2015)

Age	Number of studied fish, specimens	Prevalence, %	Infection intensity, specimens	Abundance index, specimens
3+	-	-	-	-
4+	14	28,5	1-4	0,64
5+	9	33,3	1-2	0,55
6+	11	36,3	2-5	1,09
7+	8	62,5	1-5	2
9+	5	60,0	4-8	3,4
10+	4	100	2-7	4,25
	51	45,0	1-8	1,4

Table 2

Distribution of *Diphyllobothrium* latum plerocercoids in the burbot along the middle course of the Lena river (2011-2015)

Age	Number of studied fish, specimens	Prevalence, %	Infection intensity, specimens	Abundance index, specimens
5+	4	25,0	1-2	0,5
6+	8	35,5	2-5	1,3
7+	7	71,4	2-9	3,7
8+	4	100	5-11	7,7
9+	3	100	4-11	8,0
10+	3	100	8-12	10
11+	1	100	8	8
	30	66,6	2-12	4,3

Table 3

Distribution of *Tariaenophorus nodulosus* plerocercoids in the burbot along the Viliuy river (2011-2015)

Age	Fish length, mm	Number of studied fish, specimens	Prevalence, %	Infection intensity, specimens	Abundance index, specimens
3+	359	6	16,6	1	0,3
4+	375	8	25,0	1-2	0,3
5+	468	9	44,4	1-3	0,6
6+	481	11	36,3	1-3	0,6
7+	559	8	37,5	1-3	0,7
8+	579	5	40,0	2-3	1
9+	748	2	100	1-4	2
		49	36,7	1-3	0,6

index up to 0.75 specimens. In the burbot aged 9 years old the infection with *Triaenophorus nodulosus* plerocercoids is 100%, with the infection intensity 1 to 3 specimens, and the abundance index is more than 2 specimens. The total infestation of the burbot with triaenophorid larvae along the Lena river is 36.7%, and the abundance index is 0.67 specimens. (Table 4).

In general, the proposed work is a report of the parasites fauna of the Lena and Viliuy rivers, representing sanitary and hygienic interest, which for a long period of time are subjected to a multi-factor man-caused load. Reactions of groups of parasites to the negative influence of toxicants in Yakutia have been revealed.

In the conditions of the Lena river basin, the study of the influence of industrial pollutants on parasitic systems of freshwater fish was not possible, although a lot of work are devoted to the problems of parasites fauna, epizootology, epidemiology of fish invasive diseases in the water bodies of Yakutia [5, 10, 12, 13, 14].

Considering the great influence of the anthropogenic factor such as communal pollution, in 2011-2015, in the middle course of the Lena river in the area of Yakutsk, the Khangalassky, Namsky districts, we investigated 81 fish specimens of two species, including 51 pikes, 30 burbots by the method of complete helminthological dissection. The analysis of the research results on infestation with the larvae of diphyllobothriids and triaenophores, carried out for each species separately, reveals the widespread distribution of *Diphyllobothrium latum* and

Table 4

Distribution of *Triaenophorus nodulosus* plerocercoids in the burbot along the middle course of the Lena river (2011-2015)

Age	Fish length, mm	Number of studied fish, specimens	Prevalence, %	Infection intensity, specimens	Abundance index, specimens
5+	475	4	100	3-5	3,5
6+	497	8	75,0	2-6	3
7+	563	7	85,7	3-4	2,7
8+	590	4	100	2-5	3,2
9+	732	3	100	2-4	3,0
10+	792	3	100	4-6	5,0
11+	807	1	100	5	5,0
		30	90,0	2-6	3,3

Triaenophorus nodulosus plerocercoids along the Lena river:

The pike. When examining 51 specimens of the pike caught in the middle course of the Lena river, the infection with *Diphyllobothrium latum* plerocercoids has been found. The prevalence is 39.1%, the infection intensity is 8.29 ± 0.88 specimens.

The burbot. From the dissected 30 specimens of the burbot the prevalence 67.0% was infected with *Diphyllobothrium latum* plerocercoids, the infection intensity was 16.2 ± 2.51 larvae; with *Triaenophorus nodulosus* plerocercoids prevalence 83.5%, with the infection intensity 2.1 ± 1.24 specimens.

Along the Viliuy river 79 specimens of the burbot were examined by the method of complete helminthological dissection. According to the research, *Diphyllobothrium latum* plerocercoids have not been found in fish. Out of 79 specimens of the burbot in 36.8% of them the larval stage of *Triaenophorus nodulosus* has been found with the infection intensity 3.82 ± 1.25 specimens.

The conclusion. Thus, according to the results of investigations along the Lena river, there is the intense infection with plerocercoids of Diphyllobothrium latum in fish, potential additional hosts of diphyllobothriids, which indicates to intense contamination of this part of the river with municipal waste. The infection of fish with the larvae of *Triaenophorus nodulosus* remains at a high level. This proves favorable conditions for the full development of the communities of hydrobionts, which does not hinder the biological cycle of these cestodes.

Along the Viliuy River the prevalence with the larval stage of *Triaenophorus nodulosus* is lower, compared with the Lena river. In this river the plerocercoids of *Diphyllobothrium latum* have not been found in fish, which, in our opinion, is due to less pollution of the Viliuy river with municipal waste, the absence of intense navigation as in the Lena river. But, in comparison with the Lena River, the low infection of fish with triaenophorosis indicates significant changes in the structure of hydrobionts as a result of the man-made pollution, which leads to a decrease or complete loss of individual components of the life cycle of helminthes, as a result of which the population of the parasite infection of hosts decreases.

These studies broaden the understanding of the adaptive capabilities of various fish parasites when inhabiting a polluted environment and contribute to the further development of environmental toxicology and parasitology.

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ASSESSING AIR QUALITY DETERIORATION BY SNOWCOVER REDOX POTENTIAL

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ABSTRACT

This study is an attempt to obtain a qualitative understanding of oxygen concentrations in the winter atmospheric air of a northern city from snowcover redox potential. Snowcover is a natural accumulator of chemicals deposited from the atmosphere and is thus a good indicator of atmospheric pollution. Because the oxygen ratio in the air and snowcover is constant, changes in air oxygen levels during the winter can be qualitatively assessed from redox potentials of snowmelt water.

The redox potential in the urban snowcover was found to be about 200-250 mV lower than background. Lower snowcover Eh values within the city may suggest reduced oxygen levels in the air. The negative redox potential anomalies in the snowcover are associated with the air pollution sources and complex anthropogenic geochemical haloes.

The high level of pollution with added effects of reduced air oxygen levels deteriorates the quality of the urban environment for human health and well-being. Estimation of pollution based on negative redox potential anomalies in snowcover provides an additional means of assessing the winter air quality in urban areas.

Keywords: North, cities, snowcover, redox potential, oxygen deficiency, public health.

Introduction. The urban atmosphere is characterized by a number of factors, such as warmer air temperature compared to the surroundings and higher concentrations of gaseous pollutants (carbon and nitrogen dioxides) and particulate matter, which can cause breathing problems. Atmospheric oxygen level is one of the most important factors affecting the health and well-being of urban residents. The normal atmosphere contains approximately

Table 1

Gas composition in hailstones and snow

Sample	CO_2 / N_2	O_2 / N_2	Ar / N_2	Source
Hailstones, Switzerland	0,0200	0,293	0,0154	[18]
	0,0175	0,297	0,0164	
Snow, Antarctica	-	0,263	0,0118	[19]
Atmospheric air	0,0038	0,268	0,0120	[14]

about 21% oxygen. Animals and humans are very sensitive to atmospheric oxygen concentrations, with their vital functions impaired in response to even a slight decrease in oxygen levels. Long-term exposure to an environment with the reduced partial pressure of oxygen causes a number of adaptive changes in functioning of the respiratory and other systems to compensate for low oxygen levels [10, 11]. A syndrome of "polar stress" [5] or "polar hypoxia" [1] related to the oxygen regime of the polar atmosphere has been reported in northern Siberia and far north-eastern regions of Russia. It is therefore important to know oxygen levels in the atmosphere of northern cities where anthropogenically induced oxygen depletion adds to the health effects of the natural regime. Qualitative knowledge of oxygen concentrations in the winter atmospheric air of residential and industrial zones in the northern regions, and hence of the air quality, can be obtained by estimating the redox potential (Eh) of snow cover.

Being a natural accumulator, snow cover provides actual values of dry and wet deposition during the winter season and therefore can be used as an indicator of atmospheric pollution [9, 2, 7]. Complex geochemical anomalies are formed in the snow cover around the sources of air pollution [3].

It is generally assumed that a negligible amount of air is dissolved in solid precipitation. It is known however that accreted snow crystals may contain relatively high concentrations of gaseous constituents [16].

Matsuo and Miyaki [15] believe that the atmospheric air dissolved in supercooled water droplets, on contact with an ice surface, is enriched with CO_2 and Ar more than other gases and is completely enclosed within ice crystals, since supercooled droplets constitute nuclei of ice crystals [18]. At the same time, the oxygen to nitrogen ratios in snow and atmospheric gas remains fairly similar. This conclusion is confirmed by measurements of snow samples from the East Antarctic sites (Table 1).

Methods. Relative oxygen contents in the urban atmosphere in Yakutsk during winter were estimated by measuring the redox potential of snow cover. The constancy of the ratio of oxygen in atmospheric air and snowcover makes it feasible to estimate the change in O_2 concentration in the atmosphere from the value of snow Eh. Within the city of Yakutsk, negative anomalies of Eh (oxygen deficiency) are well identified with sources of air pollution.

Based on the evidence that the oxygen ratio in the atmospheric air and the gases in snow remain similar [14,18,19], a qualitative assessment of oxygen concentrations in the winter atmosphere of Yakutsk was made in this study by measuring snowcover redox potentials.

Snow samples for the geochemical study were collected from the city area and its vicinity in the second half of March, before the onset of snowmelt. The chemical analysis of melt water was performed in the permafrost geochemistry laboratory of the Melnikov Permafrost Institute (analysts L.Y. Boitsova and O.V. Shepeleva). The redox potential was measured using an ERP-101 electrode on an I-500 ionometric converter (ZAO KRISMAS +). It has a measuring range of -2000… to +2000 mV with a resolution of 0.1 mV and an accuracy of ± 0.7 mV.

Results and discussion. The redox potential of meltwater in the Yakutsk area was found to vary over a wide range (340 to 587 mV) and depend primarily on oxygen concentration in the atmosphere, since concentrations of other oxidants were very low. The atmospheric content of H_2S (below 0.0072 mg/m^3) in Yakutsk was too low to cause the decrease in redox potential. Other oxidants, H_2, Fe, Mn and V, had relatively high concentrations close to those observed at industrial centers, such as Stockton (England) and Pasadena (USA), but were not sufficient to affect the decrease in Eh (Table 2).

Therefore, oxygen is the main potential-controlling component producing oxidizing conditions in the Yakutsk area. Positive redox potential values are known to increase with increasing oxygen content [13].

Table 2

Concentration of main oxidants in precipitation at industrial centers and Yakutsk

Parameter	Yakutsk	Industrial cities [17]	
		Pasadena, USA	Stockton, England
Population	312,0	135,0	290,0
H2S	< 0.0072	-	-
Fe	1,218	3,2	1,7
Mn	0,050	0,03	0,1
V	0,022	0,01	0,02
Cr	0,009	-	0,008
H+	2,0•10-8	-	-
pH	7,69	-	-

Note: «-» no data.

Table 3

Chemical composition of snowcover in Yakutsk and its vicinity, 2015-2016

Parameter	City of Yakutsk, n=40			Vicinity of Yakutsk (background), n=6		
	min	max	average	min	max	average
pH	5,88	7,86	6,80	5,85	6,12	6,07
Eh	340	508	449	579	587	583
TDR	13,0	193,0	55,0	8,31	9,54	9,0
HCO3-	5,50	48,6	11,49	6,76	7,73	7,15
SO42-	0,20	14,4	3,10	0,33	0,91	0,54
NO3-	0,07	8,60	2,14	0,20	0,80	0,60
Fe3+	0,05	0,3	0,14	<0,05	0,05	<0,05
Mn4+	0,5	538,0	2,5	<0,3	12,0	<0,3
V	0,1	5,0	0,16	<0,1	<0,1	<0,1

Note: n – the number of samples.

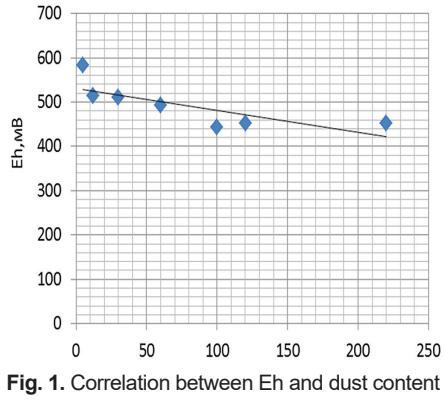

Fig. 1. Correlation between Eh and dust content in the snow cover of Yakutsk.

The measurements showed that the redox potential of the snowcover varied from 340 to 508 mV within the city, averaging 449 mV. The background values of snow Eh from the vicinity of Yakutsk (Tuymaada Valley) were 579 to 587 mV, averaging 583 mV (Table 3).

Factor analysis was used to analyze the large set of measurements in order to obtain a reliable assessment of the relationships between Eh and snow chemistry and to improve data interpretation. Classification of the Eh dependence of the parameters showed

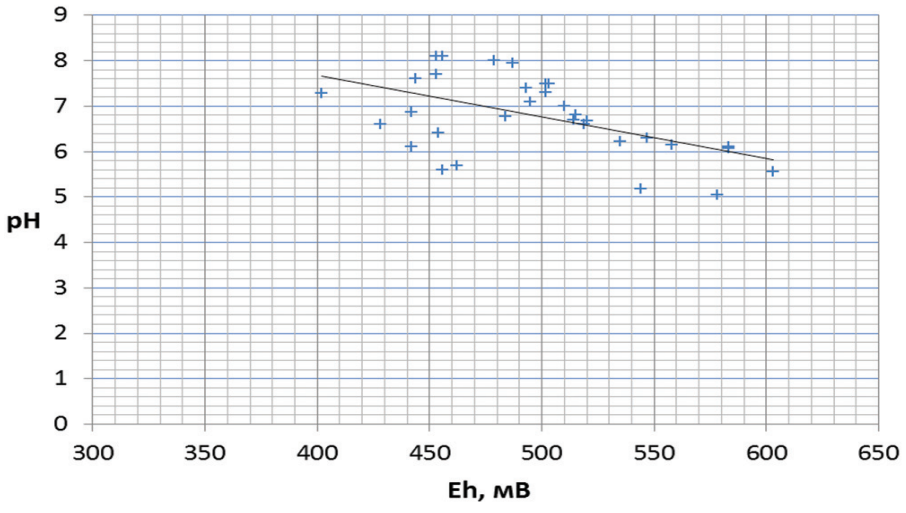

Fig. 2. Correlation between Eh and pH in the snowcover of Yakutsk

the absence of strong positive correlations and the prevalence of significant negative correlations of redox potential with major dissolved constituents of the snow cover and pH values, as well as a strong negative correlation with snow dust content (Fig. 1).

Higher alkalinity of the snowcover is observed in the areas of Yakutsk experiencing high levels of anthropogenic impact related to dust, predominantly carbonate, pollution [6]. It is therefore understandable that there is a negative correlation between Eh and pH values (the decrease in free hydrogen ions, H^+) (Fig. 2.).

It is noteworthy that the lower Eh values (reduced O_2 content in the atmosphere) and the areas of alkaline pH levels coincide with the anomalous concentrations of the main major and minor chemical constituents of the snowcover indicating anthropogenic pollution.

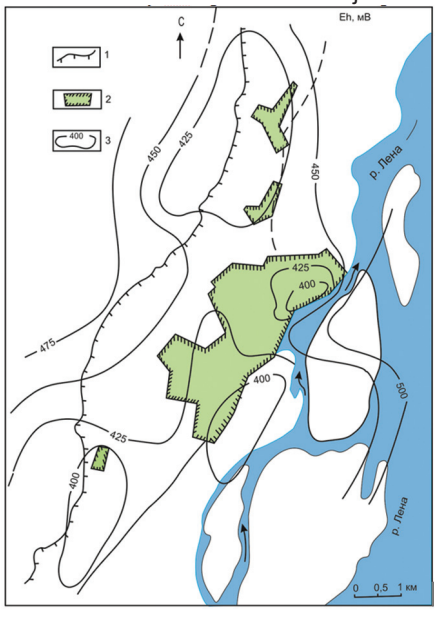

Fig. 3. Negative snow Eh anomalies in Yakutsk, 1997.
1 - Lena River valley side; 2 - urban areas; 3 - Eh isolines, mV.

Correlation analysis showed a significant negative correlation of redox potential with dust emissions (see Fig. 1). It is of interest to examine not only the total impact of dust pollution, but also the effect of minor dust constituents on the decrease in Eh (in O_2 concentration). Among the factors identified, the dust fraction of chalcophile and lithophile elements, mainly heavy metals (Mn, Pb, Zn, Ti, Cu, and Cr), showed strong negative correlations to Eh. Most of these elements are active pollutants of the atmospheric air in Yakutsk. They form strong anthropogenic anomalies in the urban snowcover and soils which are closely associated with the pollution sources [7]. The negative correlations of this group of minor elements to Eh clearly indicate that the decrease in atmospheric O_2 concentration in the areas of intense anthropogenic activity is related not only to pollution with gases and aerosols, but also to dust pollution.

The negative anomalies of Eh occur in the industrial areas of Yakutsk with high air pollution levels, such as Markha, the airport, the Electrical Power Station and the Cogeneration Station in the north, and the Modular Building Combine and the poultry factory and litter storage in the south and south-west (Fig. 3). These areas contain industry-produced geochemical anomalies which are found not only in the air, bust also in the water, soils, and vegetation [8]. The negative Eh anomalies (O_2 deficiency) also extend into the residential areas of Yakutsk. Given the high level of air pollution in the city (Air Quality Index = 5) [3], reduced oxygen concentrations are an additional factor contributing to degradation of the urban environment and related health concerns.

Low atmospheric O_2 levels can have more serious health effects during occasional warmer days in the winter brought by cyclones, when hypoxia may develop and progress in patients with cardiovascular or lung impairments [4, 10].

Conclusions. The atmospheric oxygen regime is one of the important environmental health factors for northern cities. Since the oxygen ratio in the air and snowcover is constant, changes in air oxygen levels during the winter can be qualitatively assessed from redox potentials of snowmelt water.

The negative anomalies of Eh in the snowcover of Yakutsk show clear correlations with the anthropogenic haloes of major and minor constituents in snow, alkaline pH values, dust emission levels, and anomalies of chalcophile elements (Mn, Pb, Zn, Cr, and Cu) in the dust phase of snow.

The average value of snow redox potential is 349 mV within the city and 583 mV in the surrounding area (background). The level of negative redox potential anomalies is 20–25% lower in the urban area compared to the background. Significantly lower values of snow Eh within the city may indicate reduced O_2 contents in the urban atmosphere.

The negative anomalies of snow redox potential are clearly associated with the known industrial sources of air pollution in the city and resulting geochemical anomalies. They are mainly confined to the industrial areas, but partially cover the residential areas as well.

Oxygen deficiency in the air together with the high pollution levels in the city of Yakutsk contributes to deterioration of the environmental quality for human health and well-being.

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ACTUAL TOPIC

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POPULATION DISABILITY AND SOCIO-ECONOMIC FACTORS

ABSTRACT

The purpose of the research is to study the state of primary disability (PD) in the adult population and determine its relationship with socio-economic indicators.

Materials and methods of research. The PD indicators of the adult population in the Irkutsk region are analyzed for the period of 2000-2017, according to the reporting forms No. 7-sobes The research uses statistical, graphical, and correlation methods (the Pearson coefficients are calculated using 14 socio-economic indicators).

Results and discussion. The PD indicators of the adult population in the Irkutsk region for all the causes, except the malignant tumors, ear diseases and HIV, decreased within the period of 2000-2017. The total PD indicator decreased by 30.4%: from 107.8 per 10 000 people in 2000 to 75.0 per 10 000 people in 2017

The main causes of primary disability of the adult population in the Irkutsk region include: malignant neoplasms, circulatory system diseases, and mental disorders. The PD indicators in the Irkutsk region significantly exceeded the all-Russian indicators (for $p \leq 0.05$) for 9 causes of disability in 2016: HIV (7.0 times), ear diseases (3.3 times), effects of injuries (2.5 times), mental disorders (2.2 times), tuberculosis (1.8 times), etc.

The proportion of adult people with primary disability in the 2nd group decreased both in the Irkutsk region and in the entire Russian Federation, and the proportion of those in the 1st and 3rd groups increased. As compared to the situation in 2000, where more people in the region were in the 2nd group of disability (58.3%), in 2006, the 3rd group (48.3%) started to prevail. The retirement age people continue to predominate in the age structure of the primary disability of the adult population. However, since 2006 the second place has been taken by the middle-aged people, rather than the young.

Conclusion: The research showed that the Irkutsk region is an unfavorable entity due to the primary disability of the adult population caused by HIV, mental disorders, the effects of injuries, eye diseases, etc. Strong correlations were found between 9 individual PD indicators of the adults in the Irkutsk region and socio-economic indicators.

Keywords: primary disability, adult population, socio-economic indicators.

Introduction. According to the WHO estimates, about one billion people live with disability, and this number will increase with the population ageing and the spread of chronic health disorders [3]. Apart from morbidity, the level of disability is affected by a variety of factors [6], including socio-economic ones: the incidence of disability in low-income countries is higher than in high-income countries. As compared to the people who are not disabled, people with disabilities, especially those living in developing countries, have poorer health, suffer from a higher level of poverty, and participate in the education and employment system less [3].

The purpose of the research is to study the state of primary disability (PD) in the adult population of the Irkutsk region and determine its relationship with

socio-economic indicators.

Materials and methods of research. The PD indicators in the adult population (18 years and older) of the Irkutsk region are analyzed for 16 causes for the period of 2000-2017, according to the reporting forms No. 7-sobes, the Federal Bureau of the ITU and Rosstat. The research uses statistical, graphical, and correlation methods. The ranking is carried out in the descending order. The Pearson coefficients are calculated between certain PD indicators and 15 socio-economic indicators.

Results and discussion. For the first time, within the period of 2000-2017, over 351890 people in the Irkutsk region at the age of 18 and older were declared disabled. The PD indicator of the adult population in the Irkutsk region decreased by 30.4%: from 107.8 per 10 000 people in 2000 to 75.0 per 10 000 people in 2017, with an average rate of decline of 2.1%. Thus, the total PD indicator of the adult population in the Irkutsk region tends to decrease, as well as in the other territories of Russia [2, 6]. The average long-term PD indicator of the adult population in the region in 2000-2016 exceeded a similar all-Russian indicator by 13.3% (103.9 and 91.7 per 10 000, respectively).

For most of the individual causes, the PD indicators of the adult population in the Irkutsk region also decreased in 2000-2017 (Table 1). The average annual rate of decline was between 0.4 and 11.3%. The growth of primary disability in the adult population of the Irkutsk region for the studied period was registered only for two causes: malignant neoplasms and ear diseases. Moreover, the indicator of the adult population primary disability in the region due to HIV increased from 0.05 in 2006 to 3.16 per 10 000 in 2017, with an average rate of growth of 46.7%.

In 2000, the PD indicators in the Irkutsk region exceeded the all-Russian indicators for all the causes of disability, except the diseases of the circulatory system and malignant neoplasms. In 2016, the PD indicators of the adult population in the Irkutsk region corresponded to the level of the all-Russian indicators (diseases of the endocrine system, occupational diseases), for all the other causes exceeded it. What is more, there was a significant excess of the all-Russian indicators registered (for $p \leq 0.05$) for 9 causes of disability: HIV (7.0 times), ear diseases (3.3 times), effects of injuries (2.5 times), mental disorders (2.2 times), tuberculosis (1.8 times), diseases of the nervous system (1.6 times), diseases of the musculoskeletal system (1.5 times), all causes (1.4 times), malignant neoplasms (1, 2 times).

The high level of primary disability of the adult population is explained by the number of primary disability causes in the adult population, according to which the Irkutsk region is annually included in the first ten unfavorable entities of the Russian Federation, from 5 to 9. Thus, in 2016, the Irkutsk region was in the top ten entities-outsiders for the following primary disability causes in the adult population: HIV and ear diseases (1st place); mental disorders and consequences of occupational injuries (2nd), effects of injuries (3rd), diseases of the nervous system (4th), diseases of the musculoskeletal system and all causes (5th), diseases of the digestive system (8th). In some years the region was included in the top ten unfavorable entities for 3 more reasons: endocrine system diseases, respiratory diseases and occupational diseases.

For the period of 2000-2017, the structure of the adult population primary disability in the Irkutsk region changed:

1) in 2000-2014, the first place was taken by the circulatory system diseases; in the last three years (2015-2017), these were the malignant neoplasms, since the share of the circulatory system diseases decreased from 35.0 to 23.7% during the studied period, and the proportion of the malignant neoplasms, on the contrary, increased from 10.6 to 29.7%, as well as in the other regions of Russia [2, 4];

2) first, the injuries took the third place (2000-2004); then the 4th (2005-2015), and the 5th place (2016-2017);

3) mental disorders started to take the third place (2016, 2017); before that, they were in the 5th place practically all the time; moreover, the specific value of this cause in the primary disability structure changed only by tenths of a percent: in 2000 - 6.7%, in 2017 - 6.9%;

4) at the beginning of the studied period, the musculoskeletal system diseases were in the 4th place (2000-2004), then in the last 10 years they occupied the 3rd place (2005-2015), in the recent years they returned to the 4th place (2016-2017).

In 2000, 12.8% of people in the Irkutsk region over the age of 18 were classified as the 1st disability group for the first time, 58.3% - as the 2nd group, 28.8% - as the 3rd group, which means that at the beginning of the studied period, there were more people with primary disability from the 2nd group [6]. Since 2006, the third group of disability has prevailed: in 2006 - 10.5; 41.2 and 48.3%; in 2016 - 20.5; 33.2 and 46.3%; in 2017 - 20.3; 33.3 and 46.3%, respectively. In the Russian Federation, the proportion of people with primary disability in the 1st group in 2000 was equal to 12.6%, the 2nd group - 63.3%, the 3rd group - 24.1%; in 2016 - 19.0; 37.1 and 43.9%, respectively. Thus, in the Irkutsk region, as well as in the Russian Federation as a whole, the proportion of adult people with primary disability from the 2nd group decreased, while the proportion of people from the 1st and 3rd groups increased.

In 2000, the adult population with primary disability in the Irkutsk region comprised the following age groups: the first place was taken by the retirement age people (42.1%), the 2nd place - by the young (36.5%), the 3rd - by the middle-aged people (21.4 %). The age structure of the primary disability of the adult population changed in 2006 as well - the second place was taken by the middle-aged people, rather than the young, as in 2000-2005. In 2017, the retirement age people accounted for 53.4%; the middle-aged people - 24.1% and the young, working people up to 44 years old - 22.5%. Consequently, the retirement age people continue to predominate in the age structure of the primary disability of the adult population.

An important element to improve

Table 1

PD indicators of adult population of the Irkutsk region in 2000-2017 (per 10.000, average annual growth rate / decrease, %)

Causes of disability	2000	2017	$\bar{O}_{2000-2017}$
All reasons, incl.	107,8	75,0	-2,1
Tuberculosis	6,3	2,0	-6,5
HIV*	…	3,2	-
Malignant neoplasms	11,4	22,3	+4,0
Diseases of the endocrine system	5,1	1,3	-7,9
Mental disorders	7,2	5,2	-2,0
Diseases of the nervous system	3,4	3,2	-0,4
Eye diseases	3,8	1,6	-4,8
Ear diseases	1,5	3,4	+5,1
Diseases of the circulatory system	37,7	17,7	-4,3
Diseases of the respiratory system	5,0	1,3	-7,5
Diseases of the digestive system	2,0	1,8	-0,7
Diseases of the musculoskeletal system	8,0	5,0	-2,8
Diseases of the genitourinary system*	…	0,8	-
Effects of injuries	11,3	4,7	-5,0
Effects of occupational injuries	1,3	0,2	-10,0
occupational diseases	0,7	0,1	-11,3

* reports since 2006

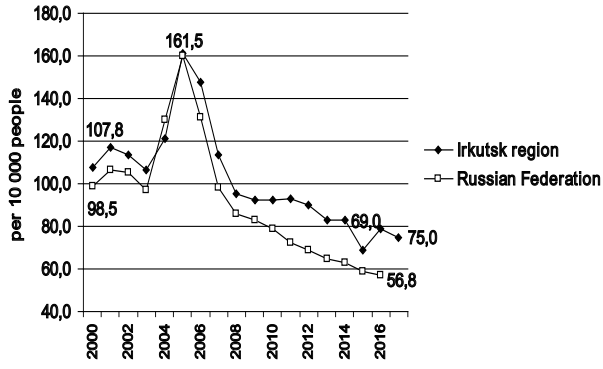
the medical care and make managerial decisions is the identification of risk areas for primary disability of the adult population [2]. In 2016, 10 municipalities were ranked as the risk territories of the Irkutsk region, where the indicators exceeded the regional level more than 1.2 times: Katangsky district (117.4 per 10 000), Bayandayevsky district (113.7) , Nukut district (113.2), and others. In 2017, 10 risk areas were recorded as well: Mamsko-Chui (104.3 per 10 000), Ust-Ilim (99.9), Ehirit-Bulagatsky (97.2) districts, etc.

The primary disability reduction in the adult population can be influenced by many factors, including socio-economic factors. Studying the influence of a number of factors on disability, A.M. Allenov found out that the demographic indicators accounted for about 10% in the total information content of all indicators, while socio-economic indicators accounted for 53%, and health system resources - for 37% [1].

According to the rating agency "RIA Rating" of the media group MIA "Russia Today," in the last 5 years, the Irkutsk region has traditionally taken low places in terms of the life quality of the population in the ranking of the Russian Federation entities from the best to the worst – the 69th, in 2015 – the 67th [5]. The rating considers a set of 72 indicators, divided into 11 groups which characterize the main aspects of the life quality in the region: the level of income of the population, employment and labor market, housing conditions, safety of living, demographic situation, environmental and climatic conditions, health of the population, the level of economic development, etc.

In 2016, among 85 entities of the Russian Federation, the Irkutsk region occupied the 20th place (17839 rubles) in terms of the average pensions; the 21st place in terms of investments in fixed assets (87807 rubles / person) and the average nominal monthly accrued salary (35510 rubles); the 22nd place in terms of the gross regional product per capita (443298 rubles); the 31st place according to the subsistence minimum of the able-bodied population (10642 rubles); the 47th place according to the Gini coefficient (0.372); the 58th place in terms of the total area of residential premises for 1 person (24.2 m^2); and the 64th place in terms of the monetary incomes per capita (22268 rubles). Judging by the resource health indicators, the rating positions of the Irkutsk region were as follows: the number of beds - the 7th place (105.4 for 10 000 people), the number of doctors – the 39th place (46.9); the number of nurses – the 43rd place (110.8). The available data say that the Irkutsk region lost some of its rating positions in 2017: the investments in fixed assets – the 22nd place (96471 rubles); the size of the subsistence minimum of the able-bodied population - the 37th place (10648 rubles), the average income per capita - the 66th place (22412 rubles); the Gini coefficient - the 45th place (0.371).

It should be noted that despite the improvement of one of the poverty indicators in the Irkutsk region, the percentage of people whose income is below the subsistence minimum decreased from 35.5% in 2000 to 20.0% in 2017. According to this indicator, the region occupied the 11th place among the unfavorable entities of the Russian Federation in 2017. According to the unemployment rate, the region took the 14th place among the disadvantaged entities, both in 2016 (8.8%, the Russian Federation - 5.5%), and in 2017 (8.7%, Russian Federation – 5.2%).



Dynamics of PD indicators of the adult population of the Irkutsk region and the Russian Federation over the period of 2000-2017 (per 10 000 people)

During the correlation analysis, the strongest correlations were found between the socio-economic indicators and the PD indicators of the adult population in the Irkutsk region as a result of 9 causes: malignant neoplasms, the effects of occupational injuries, HIV, tuberculosis, endocrine system diseases, circulatory system diseases, respiratory diseases, the effects of injuries, occupational diseases (Table 2).

Table 2

Absolute number of the Pearson correlation coefficients between PD indicators of the adult population of the Irkutsk region and socio-economic indicators

Causes of disability	correlations		
	strong	medium	weak
Malignant neoplasms	12	2	1
Effects of occupational injuries	12	2	1
Hiv	11	2	2
Tuberculosis	10	5	0
Diseases of the endocrine system	10	4	1
Diseases of the circulatory system	10	4	1
Respiratory diseases	10	4	1
Effects of injuries	10	4	1
Occupational diseases	10	3	2
Eye diseases	0	13	2
Ear diseases	2	11	2
Diseases of the digestive system	0	11	4
Diseases of the genitourinary system	0	11	4
Diseases of the nervous system	0	10	5
Mental disorders	5	9	1
Diseases of the musculoskeletal system	0	7	8
Socio-economic indicators	correlations		
	strong	medium	weak
Cost of a minimum food package, rub.	10	6	0
Investment in fixed assets, rub. / Person	10	5	1
Income per capita, rub. / Person	10	5	1
Average monthly accrued salary, rub.	9	7	0
Subsistence min. For the whole population, rub.	9	7	0
Subsistence min. For the able-bodied population, rub.	9	7	0
Gross regional product, rub. / Person	9	6	1
Average pensions, rub.	9	6	1
Total floor area, sq.M. / Person	9	6	1
Number of beds per 10 000 people	8	7	1
Number of people with incomes below the subsistence min,%	4	8	4
Unemployment rate,%	3	8	5
Gini coefficient	2	9	5
Number of nurses per 10 000 people	1	10	5
Number of doctors per 10 000 people	0	5	11

Most medium correlations are found between the analyzed socio-economic indicators and the PD indicators of the adult population in the Irkutsk Region as a result of 6 causes: eye diseases, ear diseases, digestive system diseases, genitourinary system diseases, nervous system diseases, mental disorders. Seven medium correlations and eight weak correlations are found between the indicators of primary disability due to the musculoskeletal system diseases and the socio-economic indicators (i.e. the weak correlations prevail).

It should be noted that strong correlations were not found between certain PD indicators of the adult population in the Irkutsk region and the number of doctors. A few strong correlations (from 1 to 4) can be seen with such socio-economic indicators as the number of nurses, the Gini coefficient, the unemployment rate, and the number of people with incomes below the subsistence level (Table 2).

Conclusion. The period of 2000-2017 showed a decrease in the total primary disability indicators of the adult population in the Irkutsk region and in the indicators for the majority of causes. However, an increase is registered in primary disability due to HIV, malignant neoplasms, and ear diseases. In 2016, the region was among the first ten unfavorable entities of the Russian Federation in terms of primary disability of the adult population as a result of 8 causes (HIV, ear and mastoid disease, mental disorders, consequences of injuries, including occupational injuries, nervous system diseases, musculoskeletal system diseases, diseases of the digestive system) and all causes together.

The proportion of people in the Irkutsk region with the 2nd group of disability decreased and the proportion of people with the 1st and the 3rd disability groups increased (the latter prevails). In the age structure, the proportion of young people under 44 decreased. Currently, the first place in the structure of the causes of primary disability in the adult population is taken by the malignant neoplasms, which shifted the circulatory system diseases to the second place; the mental disorders are in the third place.

Strong correlations are found between the socio-economic indicators and primary disability indicators of the adult population in the Irkutsk region due to such causes as the malignant neoplasms, effects of occupational injuries, HIV, tuberculosis, endocrine system diseases, diseases of the circulatory system, respiratory diseases, effects of injuries, occupational diseases.

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ARCTIC MEDICINE

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MEDICAL AND ECOLOGICAL RESEARCH IN THE SAKHA REPUBLIC (YAKUTIA): HISTORY, REALITY, PROSPECTS

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ABSTRACT

The article presents a historical insight on the first medical and environmental research in the Republic, what tasks were solved and what results were obtained in a survey of the population of the Vilyui group of uluses. Medical and environmental research is nowadays of great importance, especially in light of the last precedent on the River Ireliah in summer, 2018.

To eliminate the negative impact of environmental pollution on the health of the population in the area of activity of mining enterprises, we have developed a method of medical and environmental monitoring. Medical and ecological monitoring is a dynamic study of environmental pollution with a frequency of 3 or 5 years.

Taking into account the peculiarities of the northern / Arctic ecosystems (fragility, limited capacity, short trophic chain), small number of indigenous people and a negative trend in demography (Yakuts, SIM), features of industrial development of the North, represented mainly by the mining industry, oil and gas processing enterprises (in the future) and in order to prevent the medical consequences of pollution, the priority tasks are:

1) Medical and ecological monitoring is the only uncontested and mandatory condition for mining in the Republic of Sakha (Yakutia);

2) The organization extracting minerals in the territory of the republic is obliged to finance medical and ecological monitoring, which should be established by a legal act of the Republic of Sakha (Yakutia);

3) A research and development institution engaged in medical and ecological monitoring should be equipped with modern analytical equipment and appropriate human resources.

Keywords: medical and ecological monitoring, the activities of mining enterprises, microelementoses, northern ecosystems, the Arctic.

Introduction. In accordance with the priorities of the draft Strategy for the socio-economic development of the Republic of Sakha (Yakutia) until 2030 with the definition of the main directions until 2050 (Decree of the Government of the Republic of Sakha (Yakutia) of December 26, 2016 No. 455) is going to be implemented a program of comprehensive research (KNI) of the Republic of Sakha (Yakutia) aimed at the development of its productive forces and social sphere in 2016-2020; approved by the Ministry of Education and Science of the Russian Federation of October 25, 2016; by the Federal Agency of Scientific Organizations of 26.12.2016; the Head of the Republic of Sakha (Yakutia) from 10.28.2016.

Objective. The main content of this work at this stage in accordance with the Program on Scientific and Technological Information is determined by the need to conduct comprehensive Medical and ecological monitoring of the health status of the population of the Sakha Republic (Yakutia) in the area of activity of mining enterprises. At the same time, the monitoring will be carried out with the aim of timely detecting environmental pollution and its negative impact on human health in its early stages, taking into account territorial and ethnic peculiarities, social and economic development of the republic.

Results and discussion. We have repeatedly emphasized that the activities of the mining industry are fraught with environmental pollution with the priority for the deposit being developed with heavy and rare earth metals, with their subsequent ingress through river ecosystems into the food chain: phyto-zoobenthos - fish population - floodplain vegetation - milk, domestic / wild meat animals and birds – human being, with the further development of severe somatic and neurological diseases, included in the literature under the general name microelementosis. Fresh in memory is a sad precedent with the Vilyui group of uluses, when as a result of careless negligence of the enterprises of ALROSA in the 80-90s of the last century, the incidence of abnormalities in the development of children and malignant tumors increased sharply among the population, which was explained in our studies joint with Tomsk geneticists as a manifestation of chemical mutagenesis. The incidence of endocrine pathology has also increased significantly - up to 4-6 times, pathology of the blood system - up to 2-3, cardiovascular, digestive, urinary and other organ systems - from 1.5 to 2 times. There are signs of negative trends in demographic indicators of the population [1].

As expected, in human biological environments - in hair and in blood, the content of microelements, which represent a natural geochemical background, and microelements, which are part of the kimberlite of the Verkhnemunsky kimberlite field, which includes diamond deposits in the Vilyui River basin, significantly increased. Thus, the level of manganese in human blood exceeded its standard values by 3-4 times, aluminum - by 2.5; in the hair - silver - 2-3 times or more, boron - 2 times, aluminum, manganese, nickel, titanium, chromium - many times their standard values.

The data obtained indicated that:

1) the activity of diamond-mining enterprises led to the pollution of the Vilyuy River's ecosystem with microelements that are part of kimberlite and elements of the natural geochemical background of the province;

2) technogenic pollutants in the form of heavy rare-earth metals are involved in the ecological / food chain with their accumulation in the human body with the development of severe somatic and neurological pathology of man.

From the literature it is known that microelements, as a result of industrial environmental pollution, affect the living cell and the organism as a whole, primarily by:

1) influencing the genome of the living cell;

2) suppression of immunological reactivity, where their action is carried out by activation of recessive genes;

3) effects on various enzymatic and metabolic processes that constantly occur in a living organism [2-7].

Significant changes occurred in the parameters of immunological homeostasis: in more than ½ of all the examined, indicators of both cellular, and humoral and natural immunity were sharply reduced. The changes were most pronounced in terms of the T-system of immunity, phagocytosis and humoral protection of the body (Ig A, Ig M). As in the analysis of morbidity, immunological homeostasis suffered depending on how far from the sources of pollution the population lived. Thus, the indicators of the T-system of immunity in the village of Suldyukar were reduced in 40.7%, in the village of Bordon - in 36.5%, in the village of Jarkhan - in 28.9% of the examined, the phagocytic activity of leukocytes in the village of Syuldyukar was suppressed in 75.0 %, in the village of Bordon - in 37.7%, in the village of Zharkhan - in 29.0% of the examined, Ig A was reduced in the village of Suldyukar - in 70.0%, in the village of Bordon - in 55.4%, in the village of Jarhan - in 39,0% surveyed. The established pattern indicates that:

1) the nature of the identified disorders of the immunological homeostasis is di-

rectly related to the level of the general morbidity of the population and determines it;

2) the degree of violation of immunological homeostasis indicators is determined by the intensity of industrial pollution - it becomes higher as it approaches the enterprises of the diamond industry and the Vilyui reservoir.

These data were obtained by the participants of the research expedition organized by the order of the Presidium of the SB RAS No. 406 of May 10, 1989. The head of the expedition department was appointed the head of the Department of Nature Protection of the Presidium of the Yakutsk Scientific Center of the SB RAS, Doctor of Biological Sciences D.D. Savvinov. The medical part of the expedition was entrusted to lead the prof. V.G. Krivoshapkin. The research results were issued in the form of a scientific report submitted to the Founder of the expedition after a thorough independent examination, in addition, the materials of the expedition were published in numerous publications as scientific articles and monographs.

The practical output of the results of the expeditions was that, in order to "restore the health of the population and the ecology of the region," ALROSA has so far paid to the budget of 8 districts of the diamond-bearing province two-percent deductions from the company's billions in profits.

The last decade is characterized by the fact that diamond mining is confidently advancing into the Arctic zone of the Republic - the Tomtorskoe deposit of rare-earth metals (niobium), the Anabarskoe diamond deposit are being developed, development of the Mangazeysky silver-mercury deposit will begin next year, etc.

It does not take into account two important factors:

1) Northern ecosystems, especially the Arctic, are characterized by a very limited ecological capacity, therefore, they are less resistant against anthropogenic and man-made pollution. Under these conditions, even minimal concentrations of pollution, accumulating in a relatively short period of time, can increase to toxic values.

2) The Arctic is the territory of compact residence of the indigenous peoples of the North (SIM). At the same time, environmental pollution and the inclusion of heavy rare-earth metals in the food chain in the conditions of northern / arctic ecosystems can in a tragic way affect the fate of the ethnic groups inhabiting them.

To eliminate the negative impact of environmental pollution on the health of the population in the area of activity of mining enterprises, we have developed a method of medical and environmental monitoring. Medical and ecological monitoring is a dynamic study of environmental pollution with a frequency of 3 or 5 years, in particular, of the river system, with priority for a given field of heavy and rare earth metals, the appearance of the same metals in human blood, the identification of clinical, functional, morphological and physiological parameters of pathology associated with shifts in microelement homeostasis and the development of human microelementosis in their early (reversible) stages, the study of the state of the immune system, Ave types of metabolism - lipid, carbohydrate, quality of life of the population, demographic indicators (fertility, mortality, life expectancy), as well as the incidence of the population.

Using the developed methodology, the first (initial) stage of medical and ecological monitoring of public health in the area of the Tomtor deposit of rare-earth metals was carried out. To this end, in the period from 2015 to 2017, the population of four villages of the Oleneksky and Anabarsky national regions was surveyed, covering 1237 people. The selection of persons for a comprehensive survey was conducted by random sampling, the coverage of the survey in the sample was not less than 70%. Three of the four villages (Zhilinda, Kharyalyakh, Olenek - Oleneksky, Yuryung-Khaya - Anabarsky districts) were settlements of the small indigenous population of indigenous peoples.

he first (initial) stage of monitoring consisted in the study of the radiation situation, the content of trace elements in the environment, the content of the same trace elements in human blood, the main indicators of immunological homeostasis - AFP, REA, gamma-IFN, IL-6, IL-18, CRP, indicators lipid, carbohydrate metabolism, adaptive capacity of the cardiovascular system according to Mayevsky, functional and morphological indicators of the main organ systems such as cardiovascular, respiratory, digestive, urinary, musculoskeletal, endocrine, hematopoietic and other, structures of morbidity of the population by organ systems, main demographic indicators - birth rate, mortality, life expectancy, etc., disability, quality of life according to the WHO QOL-100 questionnaire.

The data of the first stage of monitoring were reported at the first Republican Ecological Congress, as well as published in the press.

Investigation of food chain links for micronutrient contamination is becoming an important and indispensable condition in emergency situations. So, for example, when a dam of dredging pits and tailing dumps is broken, when a river ecosystem is polluted with microelements that are part of kimberlite and microelements that constitute the province's natural geochemical background.

A similar precedent happened in the summer of 2018, when the dam of the dredging pit on the r. Irelyah, which led to massive pollution of the Vilyui River. The accident caused concern among the public and the population of the republic. The scientific community will have to give a scientifically based conclusion on the extent of the environmental damage caused by the accident on the environment and the health of the population of the Vilyui River basin.

According to the analysis of water samples taken in the vicinity of Verkhnevilyuisk on September 14, 2018, conducted by the Testing Center of Chemical and Soil Faculties of Moscow State University, the manganese content exceeded the standard values by 26, iron - 23, aluminum - 27, copper - 31 times. While the content of barium, lead, strontium and titanium, which are part of the kimberlite of Verkhnemunskoye field, was 3 to 13 times lower than their standard values [8]. The remaining trace elements, the level of which at the peak of pollution was up to 30 times higher than their normative values, are not part of kimberlite and represent the natural geochemical background of this diamondiferous province.

The upcoming medical and ecological studies to clarify the environmental and medical consequences of the accident that occurred due to the breakthrough of the dam of dredging pits on the Irelyah river are designed to solve the following tasks:

1)To study the content in the food chain: water - fish tissue - floodplain vegetation - milk - meat of wild / domestic animals and birds - biological environments of human trace elements whose content in the water of the Vilyui River at the peak of pollution exceeded their standard values.

2)To carry out strict accounting in the riverine settlements of persons acutely ill during the period of maximum pollution of the Vilyui River. Pay particular attention to the acute pathology of the circulatory system (myocarditis, myocardiopathy), the digestive system (enteritis, acute hepatitis, pancreatitis), the nervous system (encephalitis, meningitis), the genitourinary system (pyelitis).

All these persons should take blood from a vein for trace elements whose content in the water exceeded their standard values. With positive results of blood tests and in the presence of clinical signs of acute microelementosis, arrange treatment, medical and social rehabilitation and medical examination of the victims.

Conclusion. Taking into account the peculiarities of the northern / Arctic ecosystems (fragility, limited capacity, short trophic chain), small number of indigenous people and a negative trend in

demography (Yakuts, SIM), features of industrial development of the North, represented mainly by the mining industry, oil and gas processing enterprises (in the future) and in order to prevent the medical consequences of pollution, the priority tasks are:

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COMORBIDITY OF CLINICAL SYMPTOMS OF REFLUX DISEASE WITH LIPID-METABOLIC PARAMETERS IN YAKUTS

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ABSTRACT

The aim of the study was to assess the association of clinical manifestations of reflux disease with lipid-metabolic parameters in individuals of the Yakut nationality. The study included 100 patients with gastroesophageal reflux disease of the Yakut nationality who were in the emergency room of the Republican Hospital No. 2 - the Center for Emergency Medical Care and the Gastroenterological Department of the Yakut City Clinical Hospital during 2010-2013. The share of men was 37%, women - 63%. The mean age was 46.9 (SD = 11.35) years. Preliminary verification of the diagnosis of GERD was performed according to the recommendations of the Mayo Clinic and the Montreal Consensus (2006). Statistical processing and analysis of data were performed using the IBM SPSS Statistics 19. Paired comparisons were performed using the Mann-Whitney test. To assess the relationship of the clinical symptoms of reflux disease with the components of the metabolic syndrome, a binary logistic regression method was used with forced inclusion of predictors. Determination of the relationship of clinical symptoms of gastroesophageal reflux disease with lipid-metabolic criteria in the Yakuts revealed contribution components of metabolic syndrome, in particular abdominal obesity, arterial hypertension and triglycerides in the development of dyspeptic symptoms such as bloating, heaviness in the epigastrium, esophageal (belching) and extraesophageal manifestations (night cough) of the reflux disease.

Keywords: blood pressure, lipids, metabolic syndrome, gastroesophageal reflux disease, comorbidity, logistic regression.

The urgency of issues related to the problem of comorbidity of the digestive system and metabolic syndrome (MS), currently does not require a special introduction. Gastroesophageal reflux disease (GERD) is a multifactorial disease that causes local chronic inflammation, which increases the risk of developing Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). However, not every patient with GERD develops the terrible complications mentioned above, which suggests that other inflammatory mechanisms may exist in the pathogenesis of BE and EAC. It is known that abdominal obesity, as a central component of MS, contributes to gastroesophageal reflux. Abdominal obesity, which causes systemic inflammation, is characterized by an increase in circulating pro-inflammatory cytokines, including C-reactive protein, leptin, interleukin-6, and α-tumor necrosis factor, also contributes to the development of BE and EAC [7, 8, 11]. In this regard, of particular interest is the study of the combined course of GERD and MS. Currently, there are isolated works in Russia [3-5] devoted to the comorbidity of these diseases in certain groups of the population, and the results of the research require generalization and addition.

Research objective: to evaluate the association of clinical manifestations of reflux disease with lipid-metabolic parameters in individuals of the Yakut nationality.

Materials and methods of the research. The work was carried out as part of the research project "Metabolic Syndrome and Chronic Non-Communicable Diseases among the Residents of Yakutia" (registration number of YSU: 11-01M.2009.). The study protocol was approved by the local ethical committee at the Yakut Science Center of Complex Medical Problems

of the Siberian Branch of the Russian Academy of Medical Sciences (protocol No. 24 dated June 29, 2010). All patients were aware of participation in the study and voluntarily signed informed consent. The study was conducted on the basis of the emergency treatment department of the Republican Hospital No. 2 - the Center for Emergency Medical Care and the Gastroenterology Department of the Yakutsk City Clinical Hospital during 2010-2013. Inclusion criteria were the presence of gastroesophageal reflux disease (GERD), persons of Yakut nationality and signed informed consent to the study.

The analysis included 100 patients with GERD of the Yakut nationality. The share of men was 37%, women - 63%. The mean age was 46.9 (SD = 11.35) years.

The following survey methods were conducted for all patients: filling in a specially designed questionnaire, including questions of socio-demographic characteristics, complaints, anamnestic and anthropometric data, heredity, physical activity, the presence of bad habits; biochemical blood test: glucose (mmol / l), total cholesterol (TCh), low density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TG), atherogenic index (IA) calculation by the formula : IA = (TCh -HDL) / HDL, mmol / l; esophagogastroduodenoscopy. GERD was diagnosed based on the recommendations of the Mayo Clinic and the Montreal Consensus of 2006.

Statistical data processing was performed using the IBM SPSS Statistics 19. To determine whether the data complied with the law of normal distribution, the Kolmogorov – Smirnov test was used with the Lilliefors amendment and the Shapiro – Wilk criterion. To assess the relationship of the clinical symptoms of GERD with the components of MS, a binary logistic regression method was used with the forced inclusion of predictors. Clinical symptoms were alternately taken as the dependent variable, and the independent variables were lipid-metabolic parameters: waist circumference (WC), systolic and diastolic blood pressure (SBP, DBP), TG levels, HDL cholesterol, LDL cholesterol, on an empty stomach, glucose intolerance (PPG). To compile the regression equation, we initially compared two independent samples with the non-parametric Mann-Whitney test depending on the presence of one or another clinical sign (TM Klimova, senior scientist at NEFU). At identifying of statistically significant differences in lipid-metabolic parameters, these symptoms were included for further logistic regression analysis. The quality of the binary classification was evaluated by the area under the ROC curve.

Results and discussion. According to the results of the comparison, the most statistically significant differences in metabolic parameters in esophageal (belching) and extraesophageal symptoms of the GERD (night cough), dyspeptic symptoms(bloating, heaviness in the epigastrium), as well as in the presence of snoring during sleep (Tables 1, 2) were identified. To build a mathematical model of logistic regression, the clinical symptoms of GERD are alternately taken as the dependent variable, and the independent variables are the lipid-metabolic parameters.

Of the esophageal symptoms, only with belching revealed differences in the mean values of WS, SBP, DBP, TG and LDL (Table 1). But at the same time, when applying a logistic regression analysis, the belching had a positive relationship with OT: B (SE) = 0.056 (0.013), p <0.001, Exp (B) = 1.058; level of blood pressure: SBP (SE) = 0.040 (0.013), p <0.01, Exp (B) = 1.040; DBP B (SE) = 0.091 (0.024), p <0.001, Exp (B) = 1.096 and blood lipids: TG B (SE) = 1.148 (0.331), p <0.001, Exp (B) = 3.152; LDL C B (SE) = 0.557 (0.229), p <0.05, Exp (B) = 1.745.

In a comparative assessment of non-esophageal symptoms of GERD, differences were obtained from a night cough with a level of SBP and DBP (Table 1). In individuals with a night cough, the mean values of SBP and DBP had the highest rates compared with patients without this extra-esophageal symptom. Logistic regression analysis confirmed the dependence of night cough on BP: SBP B (SE) = 0.040 (0.017), p <0.05, Exp (B) = 1.041; DBP: B (SE) = 0.064 (0.030), p <0.05, Exp (B) = 1.066.

In the patients examined by us with a feeling of heaviness in the epigastrium, more negative differences were obtained in terms of WS, BP levels, values of TG and LDL (Table 2). When conducting a logistic regression, we confirmed that the greatest contribution to the development of such a symptom as epigastric severity is played by WS (B (SE) = 0.050 (0.013), p <0.001, Exp (B) = 1,051), blood pressure (SBP: B (SE) = 0.023 (0.012), p <0.05, Exp (B) = 1.023; DBP: B (SE) = 0.054 (0.019), p <0.01, Exp (B) = 1.055) and blood lipids (TG: B (SE) = 0.866 (0.309), p <0.01, Exp (B) = 2.377; LDL: B (SE) = 0.432 (0.217), p <0.05, Exp (B) = 1,541).

In patients with complaints of bloating, the highest numbers of SBP, DBP and

Table 1

Clinical symptoms of GERD and components of MS in people of Yakut nationality

Indicator		Burn (+)	Burn (-)	p	Night cough (+)	Night cough (-)	p
WS, cm.	M (SD)	102(16,40)	84(17,39)	0,000	99(19,21)	90(18,75)	0,068
	Me (Q25-Q75)	103,5(96-113)	78(73-97)		103(83,5-113)	80(75-103)	
SBP, mmHg.	M (SD)	133 (14,67)	121 (19,29)	0,001	137(17,58)	124(18,01)	0,017
	Me (Q25-Q75)	130(120-140)	120(110-130)		135(123-149)	120(110-140)	
DBP, mmHg.	M (SD)	86 (7,44)	76 (12,67)	0,000	85,63(10,31)	78,51(11,89)	0,023
	Me (Q25-Q75)	90(80-90)	80(60-90)		90,00(80-90)	80(70-90)	
TG, Mmol/l	M (SD)	1,76 (0,91)	1,16 (0,5)	0,000	1,52(0,69)	1,37(0,79)	0,263
	Me (Q25-Q75)	1,67(1,02-2,30)	1,02(0,71-1,44)		1,44(1,01-2,05)	1,17(0,77-1,72)	
HDL, Mmol/l	M (SD)	1,34 (0,55)	1,32 (0,28)	0,368	1,25(0,35)	1,34(0,42)	0,810
	Me (Q25-Q75)	1,21(1,03-1,49)	1,29(1,14-1,52)		1,34(0,97-1,50)	1,28(1,11-1,50)	
LDL, Mmol/l	M (SD)	3,59 (0,91)	3,06 (1,02)	0,010	3,31(0,96)	3,26(1,02)	0,705
	Me (Q25-Q75)	3,82(2,89-4,18)	3,13(2,21-3,82)		3,36(2,88-4,10)	3,28(2,49-3,94)	
glucose, Mmol/l	M (SD)	5,60 (1,17)	5,22 (1,05)	0,075	5,25(1,11)	5,39(1,12)	0,851
	Me (Q25-Q75)	5,65(4,83-6,20)	5,10(4,35-5,85)		5,55(4,24-6,10)	5,20(4,67-6,18)	
PPG, Mmol/l	M (SD)	6,48 (1,25)	6,3 (1,49)	0,794	6,06(1,49)	6,54(1,31)	0,634
		6,10(5,46-7,62)	7,00(5,47-7,63)		6,02(5,05-7,32)	6,20(5,60-7,65)	

Note: WS - waist circumference; SBP - systolic blood pressure; DBP - diastolic blood pressure; TG - triglycerides; HDL – high-density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; PPG - postprandial glucose level; M – is the mean; SD - standard deviation; Me– median; Q25-Q75 - 25 and 75 quartile distributions; p - the achieved level of statistical significance of differences when comparing groups.

Table 2

Clinical symptoms of GERD and components of MS in people of Yakut nationality

Indicator		A feeling of heaviness in the epigastrium (+)	A feeling of heaviness in the epigastrium (-)	p	Bloating (+)	Bloating (-)	p	Snoring during sleep	No snoring during sleep	p
WS, cm.	M (SD)	99,5 (17,84)	84(17,00)	0,000	98 (18,19)	84 (7,58)	0,001	104(15,58)	77(10,50)	0,000
	Me (Q25-Q75)	102 (79,0-112,0)	78 (73-96,5)		100,5 (78-110,5)	79 (72-97)		104,5 (97-115)	77 (70-80)	
SBP, mmHg.	M (SD)	130 (14,63)	122 (20,82)	0,027	132(13,17)	119 (20,87)	0,000	133(13,70)	117(17,89)	0,000
	Me (Q25-Q75)	130 (120-140)	120 (110-140)		130 (120-140)	120 (100-130)		130 (120-140)	110 (105-130)	
DBP, mmHg.	M (SD)	83 (9,79)	76 (12,72)	0,005	84 (8,26)	76 (3,58)	0,001	86,5(7,16)	72(11,59)	0,000
	Me (Q25-Q75)	85 (80-90)	80 (60,0-90,0)		87,5 (80-90)	80 (60-90)		90 (80-90)	70 (60-80)	
TG, Mmol/l	M (SD)	1,64 (0,93)	1,18 (0,55)	0,013	1,57(0,92)	1,23(0,57)	0,097	1,76(0,89)	1,03(0,42)	0,000
	Me (Q25-Q75)	1,51 (0,91-2,30)	1,04 (0,74-1,45)		1,39 (0,87-2,17)	1,07 (0,79-1,49)		1,64 (1,05-2,30)	0,96 (0,69-1,39)	
HDL, Mmol/l	M (SD)	1,35 (0,51)	1,30 (0,29)	0,814	1,37(0,48)	1,28(0,31)	0,368	1,36(0,49)	1,34(0,28)	0,669
	Me (Q25-Q75)	1,23 (1,05-1,50)	1,28 (1,12 -1,51)		1,30 (1,12-1,56)	1,27 (1,06-1,45)		1,26 (1,07-1,55)	1,30 (1,17-1,51)	
LDL, Mmol/l	M (SD)	3,50 (0,95)	3,08 (1,02)	0,036	3,42 (0,95)	3,12 (1,05)	0,134	3,53(1,06)	3,03(0,90)	0,012
	Me (Q25-Q75)	3,75 (2,79-4,23)	3,18 (2,26-3,83)		3,66 (2,81-4,10)	3,19 (2,34-3,85)		3,82 (2,894,40)	3,18 (2,40-3,74)	
glucose, Mmol/l	M (SD)	5,53 (1,22)	5,23 (0,99)	0,147	5,40 (1,26)	5,34 (0,95)	0,825	5,63(1,32)	5,13(0,77)	0,029
	Me (Q25-Q75)	5,60 (4,80-6,20)	5,00 (4,40-6,02)		5,40 (4,46-6,20)	5,20 (4,62-6,10)		5,90 (4,46-6,42)	5,10 (4,71-5,55)	
PPG, Mmol/l	M (SD)	6,15(1,27)	6,91 (1,34)	0,059	6,25(1,39)	6,72(1,25)	0,214	6,27(1,41)	7,02(0,86)	0,194
		5,80 (5,40-6,50)	7,53 (6,25-7,70)		5,90 (5,29-7,25)	7,20 (5,77-7,65)		6,00 (5,34-7,67)	7,25 (6,10-7,70)	

Note: WS - waist circumference; SBP - systolic blood pressure; DBP - diastolic blood pressure; TG - triglycerides; HDL – high-density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; PPG - postprandial glucose level; M – is the mean; SD - standard deviation; Me– median; Q25-Q75 - 25 and 75 quartile distributions; p - the achieved level of statistical significance of differences when comparing groups

WS were observed than in patients with no bloating (Table 2). At the same time, a positive association of the bulge with OT (B (SE) = 0.041 (0.012), p <0.001, Exp (B) = 1.042) was obtained; SBP(B (SE) = 0.042 (0.013), p <0.001, Exp (B) = 1.043); DBP (B (SE) = 0.064 (0.020), p <0.001, Exp (B) = 1.067) and triglycerides (B (SE) = 0.622 (0.290), p <0.05, Exp (B) = 1.863).

Also, a comparative analysis of lipid-metabolic parameters in the examined patients with snoring during sleep was conducted. At the same time, high lipid-metabolic indicators were obtained in the group of patients with the GERD and the presence of snoring in sleep, except for the HDL cholesterol values and postprandial glucose level (Table 2). The mathematical model of logistic regression showed the association of snoring during sleep with WS (B (SE) = 0.130 (0.024), p <0.001, Exp (B) = 1.138); SBP(B (SE) = 0.066 (0.017), p <0.001, Exp (B) = 1.069); DBP (B (SE) = 0.163 (0.035), p <0.001, Exp (B) = 1.177) and TG (B (SE) = 1.766 (0.456), p <0.001, Exp (B) = 5.848); LDL (B (SE) = 0.518 (0.228), p <0.05, Exp (B) = 1.678) and glucose (B (SE) = 0.431 (0.206), p <0.05, Exp (B) = 1.539).

Thus, assessing the relationship of clinical symptoms of the GERD with MS have Yakut nationality identified contribution abdominal obesity, arterial hypertension and triglycerides in the development of dyspeptic symptoms (bloating, weight epigastric), esophageal (belching) and extraesophageal manifestations (night cough) GERD. In accordance with the above, it can be said that lipid-metabolic disorders and abdominal obesity, and not the value of body mass index, are one of the strong predictors of GERD development. The correlation of GERD symptoms with blood pressure indicators is multifactorial, since, on the one hand, pathological gastroesophageal reflux can trigger a cascade of pathogenetic mechanisms that initiate destabilization of coronary blood flow, myocardial ischemia and cardiac rhythm disturbances [6]. On the other hand, arterial hypertension causes impaired microcirculation and hemodynamics of internal organs, as well as calcium antagonists used to treat arterial hypertension reduce the tone of the lower esophageal sphincter and suppress muscle contraction in the esophagus itself. In a comparative analysis of the treatment of arterial hypertension in our study, calcium antagonists received 14% of patients.

It should be noted that in our previous work, the analysis of the clinical picture of reflux disease showed that heartburn is the leading symptom, regardless of their ethnicity and the presence or absence of MS. In the presence of metabolic syndrome, reflux disease was characterized by polymorphism of clinical manifestations and atypical course. With the association of reflux disease and MS, regardless of the ethnicity of the patients, dyspeptic symptom complex is more often stated. The next characteristic feature of the manifestation of reflux disease in patients with metabolic syndrome was the presence of a sufficiently high frequency of non-esophageal symptoms [1, 2].

Conclusion. Analysis of the relationship of clinical manifestations of reflux disease with lipid-metabolic indicators showed that Yakuts have esophageal (belching) and extraesophageal (night cough) and dyspeptic (swelling, heaviness in epigastric) manifestations of GERD positively associated with RT, BP, TG and LDL, which at high rates increase the risk of mortality from cardiovascular and oncological complications. In this connection, the correction of lipid-metabolic risk factors is important in the treatment of GERD in persons with metabolic syndrome, that demands joint participation of specialists of cardiological and gastroenterological profile.

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DIET IN THE NORTH

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MICROBIOTA AND SANITATION OF UNDERGROUND GLACIERS DURING FOOD STORAGE

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ABSTRACT

Carrying out the relevant works on sanitation has difficulties due to the lack of effective means and scientifically-based regimes. The aim of this work is to study the microbiota and to find effective methods and regimes for the sanitation of glaciers in permafrost conditions for food storage. The work was carried out in the Laboratory for the Development of Microbial Preparations of the FSBSI the Yakut Scientific Research Institute of Agriculture, as well as in the underground glaciers of Yakutsk and the regions of the Republic of Sakha (Yakutia) in the period 2007 - 2015. The material for studying the quantitative and qualitative composition of the microbiota circulating in glaciers was air samples and scrapings from surfaces, air samples and scrapings from the glacier surfaces were collected in February, April, June, August, and November. At the same time, the external and internal air temperatures were taken into account. Air samples were taken by sedimentation method. The number of microorganisms in the air, on the surfaces was determined according to the generally accepted methods of sanitary-microbiological examination of environmental objects.

The microbiota of the underground glacier for food storage is mainly represented by soil spore-forming aerobic bacteria of the genus Bacillus, as well as toxic and mold fungi of the genera Aspergillus, Mucor and pathogens of yersiniosis, which can be dangerous in the contamination of food.

We were the first sanitation for the of the glaciers, contaminated with intestinal, coccal and spore infections in Yakutia developed effective modes of disinfection (up to -21.0±0.8°C) using electrochemically activated anolyte containing 0.1 mg/ml of active chlorine and peracetic acid in a concentration of 0.5% (ADV) at the rate of 300 ml/m2 and exposure time 5 hours, and 1% aqueous solutions of the PAA, at the rate of 300-400 ml/m2, exposure 18 hours.

Keywords: underground ice-houses, food storage, microbial contamination, sanitization.

Introduction. The whole territory of the Republic of Sakha (Yakutia) is occupied by permafrost, in which an enormous supply of cold is accumulated, which directly relates the climate to the sharp continentally and low temperatures. In the republic, for a long time and until now, storage of food raw materials and food products in glaciers is widespread. The use of natural cold in the processing and storage of food products in the conditions of Yakutia contributes to severe winter, which lasts in some of its regions up to 8-9 months and the presence of permafrost [1]. Inadequate design requirements and improper operation of underground refrigerators lead to premature deterioration of stored food and a decrease in quality [2, 6, 9]. After the ice is laid in the early spring (February-March), the glacier is loaded with products. During operation, the glacier is only opened as needed on certain days and hours. After the release of the products, at the end of November, the glacier is completely opened. Before and after operation, the glacier is mechanically cleaned.

Sanitary treatment of glaciers in most cases reduces only to mechanical cleaning of internal compartments and tambours, which leads to their high contamination by microorganisms in the process of exploitation. In the available literature there are no reports on methods and regimes for sanitation of glaciers in permafrost conditions.

In the opinion of several authors E.N. Bolotsky et al. [4], the trend of development of disinfection technology in recent decades throughout the world is not to create new disinfectants, but to search and activate already known means, in the development of regimes providing a high bactericidal effect with a minimum concentration of active substances and a weak toxic effect [4]. A technochemical activation technology has been developed in our country that allows synthesizing cheap biocidal solutions (anolytes) of the universal spectrum of action at the site of application. After use they spontaneously decompose without the formation of toxic compounds and do not require neutralization and subsequent washing. Therefore, a promising direction in the search for available sanitizing preparations is the use of biocides, which are created on the basis of unipolar electrochemical activation (ECA) of aqueous solutions of chlorides [5, 8, 13].

In the available literature it can be found an information on the use of an anodic fraction (anolyte) of an electrochemically activated (ECA) solution of 1% common salt as a disinfectant in medicine, processing industry, agriculture, fodder production, veterinary medicine [3, 14].

The minus temperature in the glacier complicates the sanitation of the ice surfaces. According to the research of N.P. Tarabukina, for the disinfection of wooden surfaces, seeded Sal. abortus equi BN-12, Str. equi N-34, Bac. subtilis TNP-3, at low temperatures up to -12°C there is an effective application of 1-3% (by active substances) solutions of peracetic acid (PAA) [15-17].

The aim of this work is to study the microbiota and to find effective methods and regimes for the sanitation of glaciers in permafrost conditions for food storage.

Materials and methods. The work was carried out in the Laboratory for the Development of Microbial Preparations of the FSBSI the Yakut Scientific Research Institute of Agriculture, as well as in the underground glaciers of Yakutsk and the regions of the Republic of Sakha (Yakutia) in the period 2007 - 2015.

The material for studying the quantitative and qualitative composition of the microbiota circulating in glaciers was air samples and scrapings from surfaces, air samples and scrapings from the glacier surfaces were collected in February, April, June, August, and November. At the same time, the external and internal air temperatures were taken into account.

Air samples were taken by sedimentation method, the surfaces were examined using scrapes taken from ice walls with a 10x10 cm stencil in sterile Petri dishes. The number of microorganisms in the air, on the surfaces was determined according to the generally accepted methods of sanitary-microbiological examination of environmental objects. The generic and species identification of the isolated cultures of microorganisms was carried out according to the "Berjee bacteria determinant" (1997), and "The determinant of zoopathogenic microorganisms" (1995). Staining of smears was prepared according to Gram. The results of microbiological cultures were taken into account after 18 and 24 hours for bacteria, and microscopic fungi after 5 days. Elective media prepared according to GOST were used: meat-peptone agar (MPA) to determine the amount of MAFAnM - mesophilic aerobic and facultative-anaerobic microorganisms; MPA - to isolate spore-forming aerobic bacteria (after heating the main dilution at 80°C for 15 minutes); Endo - for the isolation and differentiation of enterobacteria; MBTB - medium with bromotymol blue to isolate Yersinia; Czapek - for the isolation of microscopic fungi.

As test cultures there were used the strains of bacteria Salmonella abortus equi BN-12, Streptococcus equi N-34, Bacillus subtilis TNP-3, which have been certified by the All-Union State Scientific and Control Institute of Veterinary Preparations (Moscow).

Preparations of solutions, determination of the active substance, disinfection quality control were carried out according to the "Rules for disinfection and disinvasion of objects of state veterinary supervision" (2002). To obtain an electrochemically activated neutral anolyte, an apparatus for the electrochemical synthesis of activated disinfecting solutions of AQUAEHA (mod. 40) of STEL type was used.

Results of the research. The total microbial contamination on the surface of the walls of glaciers is from $2.8x10^2$ to $60.0x10^3$ CFU/m^3. The total microbial contamination of the glacier air ranges from $1.4x10^2$ to $23.6x10^3$ CFU/m^3. The air temperature of the glacier during the study period remained stable and averaged 13.4 ± 2.1°C, regardless of the outside air temperature.

From the microbiota of the underground glacier spore-forming aerobic bacteria of the genus Bacillus were isolated in an amount from $1.1x10^2$ to $43.3x10^3$ CFU/cm^2, related to the soil saprophyte microflora. In addition, the causative agents of yersiniosis (from $1.5x10^2$ to $23.6x10^3$ CFU/cm^2) have been identified, related to sapronoses, which are classified as species: Yersinia pseudotuberculosis and Yersinia enterocolitic. Yersinia refers to psychotrophic bacteria with a wide range of adaptive and pathogenic properties. Researchers G.P. Somov, V.U. Litvin [12], E.M. Lenchenko [7] revealed the laws of the existence and circulation of Yersinia in the communities of the environment and believe that soil and aquatic ecosystems are obligatory components of natural foci of sapronoses. In this regard, the identification of the causative agents of yersiniosis in the microbiota of glaciers in the conditions of the cryolithozone confirms the authors' opinion and widens the range of their distribution.

Yersinia are steady to cold, well stand the temperature from -15 up to -20 °C, and in these conditions can exist for a long time. Psychrophilic properties of Yersinia pseudotuberculosis contribute to the emergence and development of the epidemic process, because the cold not only allows these bacteria to multiply and accumulate in environmental objects, but also is the trigger factor of the genetic and biochemical mechanisms that ensure the regulation of their virulence [11, 18]. Therefore, the pathogens of yersiniosis isolated from the surfaces of glaciers present the danger of food contamination

Results of industrial experiments on the disinfection of ice surfaces, (glacier temperature -21.0±0.8°C)

Disinfectants	Concentration of active substance (in %)	Consumption	Growth of microorganisms														
			Exposition (in hours)														
			1,5			3			5			18			24		
			Sal. abortus equi BN-12	Str. Equi N-34	Bac. subtilis TNP-3	Sal. abortus equi BN-12	Str. Equi N-34	Bac. subtilis TNP-3	Sal. abortus equi BN-12	Str. Equi N-34	Bac. subtilis TNP-3	Sal. abortus equi BN-12	Str. Equi N-34	Bac. subtilis TNP-3	Sal. abortus equi BN-12	Str. Equi N-34	Bac. subtilis TNP-3
PAA	1	300 ml/m²	-	-	+-	-	-	+-	-	-	+-	-	-	-	-	-	-
PAA	1	400 ml/m²	-	-	+-	-	-	+-	-	-	+-	-	-	-	-	-	-
PAA	1	500 ml/m²	-	-	+-	-	-	+-	-	-	-	-	-	-	-	-	-
Anolyte neutral with an active chlorine content of 0.5 mg/ml		200 ml/m²	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anolyte neutral with an active chlorine content of 0.5 mg/ml + PAA	0,5	300 ml/m²	-	-	+-	-	-	+-	-	-	+-	-	-	+-	-	-	+-
Anolyte neutral with an active chlorine content of 0.1 mg/ml + PAA	0,5	300 ml/m²	-	-	+-	-	-	+-	-	-	-	-	-	-	-	-	-
Tap water	Control	300 ml/m²	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Note: PAA - Peracetic acid, ADV-active ingredient, (+) - growth of test cultures; (+ -) - single growth of test cultures; (-) - no growth of test cultures.

during storage.

Also, the results of our studies indicate the presence of toxigenic and mold species of the genera Aspergillus and Mucor in the microbiota of glaciers at temperatures from -14 to -22°C, although, according to the published data, the criterion for the temperature existence of microscopic fungi is up to -9°C [10].

The results obtained allow us to conclude that it is necessary to find effective measures for the rehabilitation of underground glaciers used for food storage.

For the first time for the sanitation of glaciers have been tested an electrochemically activated neutral anolyte with a content of 0.5 mg/ml and 0.1 mg/ml of active chlorine, with the addition of 0.5% peracetic acid (PAA), as well as 1% peracetic acid solutions (PAA), at a flow rate of 200-500 ml/m², an exposure of 1.5; 3; 5; 18 and 24 hours. As a control, ice surfaces contaminated with test cultures are treated with tap water, at a rate of 200-500 ml/m². Solutions are applied in the form of small-drop spraying with a non-propellant balloon at a glacier temperature of -21.0±0.8°C. The results are shown in Table.

As the data in Table show, 1% solutions of PAA, at a flow rate of 300-400 ml/m², an exposure of 18 hours, reliably disinfect the ice surfaces contaminated with intestinal, coccal, spore infections. When the flow rate increases to 500 ml/m² an exposure of a harmful effect on Sal. abortus equi BN-12, Str. equi N-34, Bac. subtilis TNP-3 is reduced to 5 hours. It should be noted that the use of a large number of solutions is not desirable for the sanitation of glaciers.

According to the results of the research, solutions of anolyte neutral with an active chlorine content of 0.5 mg/ml, with the addition of 0.5% PAA, the ice surfaces contaminated with Sal.abortus equi BN-12, Str. equi N-34, Bac.subtilis TNP-3 are not completely disinfected, and the use of dilute solutions of anolyte neutral with an active chlorine content of 0.1 mg/ml with the addition of 0.5% PAA, at a flow rate of 300 ml/m², starting with a 5-hour exposure completely destroy these microorganisms.

Conclusion. Thus, the study showed that in the underground glaciers used for food storage (with an additional installation for maintaining the cold), at a temperature of -13.4±2.1°C, the total microbial contamination on surfaces is up to 60.0×10³ CFU/cm² and in air - up to 23.6x10³ CFU/m³. From the microbiota of the underground glacier in winter (February-April), the yersiniosis pathogens Yersinia pseudotuberculosis, Yersinia enterocolitica and toxigenic fungi of the genus Aspergillus (fumigatus, niger, mucor sp.) had been isolated.

We were the first sanitation for the of the glaciers, contaminated with intestinal, coccal and spore infections in Yakutia developed effective modes of disinfection (up to -21.0±0.8°C) using electrochemically activated anolyte containing 0.1 mg/ml of active chlorine and peracetic acid in a concentration of 0.5% (ADV) at the rate of 300 ml/m² and exposure time 5 hours, and 1% aqueous solutions of the PAA, at the rate of 300-400 ml/m², exposure 18 hours.

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SCIENTIFIC REVIEWS AND LECTURES

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GENETIC POLYMORPHISMS OF THE HEMOSTASIS SYSTEM

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ABSTRACT
Despite advances in treatment of chronic viral hepatitis, search of predictors of poor outcome is still needed. One of them is the hemostasis system. The decoding of the human genome has made it possible to determine genetic markers that lead to blood coagulation disorders. It is widely known that more than 10 single nucleotide polymorphisms (SNP) are responsible for some form of coagulation disorders. The genome-wide

association study (GWAS) has only come to the fore recently, and expansion of the roster of hemostasis genes is now possible.

Thrombophilia has a special role in the inherited disorders of hemostasis. The view of the role of thrombophilia changed since *FV Leiden*, *FII* and Antiphospholipid syndrome (APS) mutations were discovered. It was found that genetic anomalies of hemostasis cause thrombosis in 80-90 per cent of cases.

FGB, FII, FV, FVII, FXIII, ITGA2, ITGB3, MTHFR, PAI-1 and other genes of hemostasis are presented in the article. The article describes the role of these genes by developing thrombosis and thrombophilia, and considers protective SNPs.

A shared vision of the desired conditions of hemostasis genes affect chronic liver disease needs to be developed. Pathophysiological and biochemical mechanisms of allelic variants in thrombophilia genes of chronic liver disease are not exactly conventional. A better understanding of the role of hemostasis genes' allelic variants of processes of intrahepatic epithelium is essential for prognosis of the impact in the liver disease, treatment and clinical background.

Keywords: hemostasis system, coagulopathy, coagulation disorders, genetic factors, predisposition.

Relevance. According to WHO, 325 million people in the world have viral hepatitis, hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 80% of hepatocellular carcinoma cases. Viral hepatitis related mortality is 1.34 million deaths per year, which is comparable to HIV/AIDS, tuberculosis and malaria [23]. In the Russian Federation the total number of people living with HBV and HBsAg carriers are estimated to be 5 million, the overall number of HCV infections at least 2 million people. According to Register "Chronic viral hepatitis in the Republic of Sakha (Yakutia)" 14 805 people with chronic viral hepatitis were registered since October 2017. A total of 6320 people had been registered as having HBV, 6619 – HCV, 1048 – HDV (hepatitis D virus), 646 – mixed infection, 382 patients with cirrhosis and 26 patients with primary liver cancer [2].

Since 1991, the program of WHO for immunization of the population from HBV is implemented in Russia. Antiviral therapy of viral hepatitis develops, but the incidence remains at the previous level. Despite advances in treatment of chronic viral hepatitis, search of predictors of poor outcome is still needed with a view to improving personalized therapy. One of them is hemostasis system. Hemostasis disorders at chronic liver disease lead to coagulation imbalance, at the same time it affects both primary and secondary hemostasis. Disruption of the hemostasis system in chronic liver diseases leads to a coagulation imbalance, and this affects both vascular platelet and coagulation hemostasis.It can lead either to bleedings, or to thromboses.

A genome-wide association study (GWAS) has only come to the fore recently. GWAS is an observational study of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait. GWASs typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major human diseases, but can equally be applied to any other genetic variants and any other organisms. Each person gives a sample of DNA, from which millions of genetic variants are read using SNP arrays. If one type of the variant (one allele) is more frequent in people with the disease, the variant is said to be associated with the disease. The associated SNPs are then considered to mark a region of the human genome that may influence the risk of disease [27].

SNPs of hemostasis system genes

Genes	Localization	SNPs	Allels	Effects
FGB	*4q31.3*	*C148T*	*T*	high level of fibrinogen in blood, increase in probability of blood clots formation
			C	normal level of fibrinogen in blood
FII	*11p11.2*	*G20210A*	*A*	high level of a prothrombin in blood, increase in probability of blood clots formation
			G	normal level of prothrombin in blood
FV	*1q24.2*	*G1691A*	*A*	steady active form of FV to action of enzymes that leads to hypercoagulation
			G	normal coagulation
FVII	*13q34*	*G10976A*	*A*	decrease in probability of thromboses
			G	normal coagulation
FXIII	*6p25.1*	*G103T*	*T*	decrease in probability of thromboses
			G	normal coagulation
ITGA2	*5q11.2*	*C807T*	*T*	increase in speed of adhesion of platelets that results in the increased risk of thrombophilia.
			C	normal coagulation
ITGB3	*17q21.32*	*T1565C*	*C*	increase in speed of platelet adhesion, low efficiency of acetilsalicylic acid
			T	normal coagulation
MTHFR	*1p36.22*	*C677T*	*T*	folate cycle disorders, cardiovascular diseases
			C	normal level of folat
PAI-1	*7q22.1*	*5G(-675)4G*	*4G*	decrease fibrinolytic activities, increased probability of blood clots formstion
			5G	normal fibrinolytic activities

Due to interpretation of human genome structure it became possible to define the genetic markers causing hemostasis system disorders. Markers which are revealed by molecular genetic analysis represent variants of genes that cause changes of gene activity or modification of protein product. In certain conditions it can lead to hemostasis system disorders [27]. Thrombophilia has the special role in the inherited disorders of hemostasis. Barkagan Z. S. and Momot A. P. (2001) define thrombophilia as disorders of hemostasis and hemorheology, which are characterized by the increased tendency to thrombose occurance with ischemia in blood vessels [9]. The overall picture of the role of thrombophilia in the pathogenesis of thrombosis changed after *FV Leiden*, *FII* and Antiphospholipid syndrome (APS) mutations were discovered.

Today, more than 10 SNPs of hemostasis system are widely known (Table 1).

Genetic polymorphisms of fibrinogen. Fibrinogen is made and secreted into the blood primarily by liver hepatocyte cells. Endothelium cells are also reported to make what appears to be small amounts of fibrinogen but this fibrinogen has not been fully characterized; blood platelets and their precursors, bone marrow megakaryocytes, while once thought to make fibrinogen, are now known to take up and store but not make the glycoprotein. The final secreted, hepatocyte-derived glycoprotein is composed of two trimers with each trimer composed of three different polypeptide chains, the fibrinogen alpha chain (also termed as the Aα or α chain) encoded by the FGA gene, the fibrinogen beta

chain (also termed as the Bβ or β chain) encoded by the FGB gene, and the fibrinogen gamma chain (also termed as the γ chain) encoded by the FGG gene. All three genes are located on the long or «p» arm of human chromosome 4.

T. Cronjé et al (2017) studied 6000 representatives of the people of Tswana living in South Africa. They found that *FGB (854A)* and *FGG (rs1049636)* were significantly connected with the general fibrinogen, and *FGA (rs2070011)* related to high concentrations of fibrinogen γ among indigenous people of South Africa. FGB (-148T) was associated with a large diameter of fiber, and *FGA* was associated with high concentrations of fibrinogen. In this research, *FGA (rs2070011)* and *FGG (rs1049636)* were less significant in terms of their influence on the maximum absorption [15].

A.P. Reiner et al (2006) studied 5115 Euro-Americans and showed what rs1049636 in 9 *FGG* (C-allele) introne and rs1800791 (minor A-allele) in primotor *FGB* are connected with increase in the general level of fibrinogen [4]. SNP rs1800791 increase the levels of fibrinogen by linking nuclear proteins with the *FGB* promotors (Van't Hooft et al, 1999) [33]. Lovely et al (2011) studied 5124 people of European origin, and found SNPs rs7681423 and rs1049636 located in the field of fibrinogen splaysing in 9th intron of *FGG* gene. It is the second most important SNP which is connected with fibrinogen levels. In addition, there was a relation between high levels of fibrinogen and rs2070011 in the field of FGA promotor [3]. However, as a result of studies of 3891 Europeans, Mannila M.N. et al (2006) obtained contradictory results: decrease in levels of fibrinogen was related with increase in number of alleles [13].

Unlike previous studies showing connection between levels of fibrinogen and other SNP in intron 9 of *FGG*, rs2066865 and rs13800791 in the field of *FGB* promotor (Mannila et al, 2007), R.C. Kotzé et al (2015) did not find connection between rs1049636 *FGG*, rs2070011 *FGA* and properties of the clot, which shows that the observed differences are result of genotypes differences of fibrinogen levels. Other SNPs analyzed in this research (rs1049636 and rs2070011) also did not have association with properties of the clot. Observed increase in the maximum absorption can be result of increase in concentration of fibrinogen for rs1800787, though it cannot be proved because of small amount of samples of alleles homozygous minor carriers [19].

Genetic polymorphisms *G20210A* (rs1799963) of *FII.* The F2 gene encodes the prothrombin protein (also called coagulation factor II). Prothrombin occurring in blood plasma is an essential component of the blood-clotting mechanism. Prothrombin is transformed into thrombin by a clotting factor known as factor X or prothrombinase; thrombin then acts to transform fibrinogen, also present in plasma, into fibrin, which, in combination with platelets from the blood, forms a clot.

SNP *G20210A* is caused by replacement of the nucleotide of guanine (G) by adenine (A) in *FII* gene position 20210; it leads to the raised gene expression in A-allele. The surplus production of prothrombin is risk factor of myocardial infarction, thromboses, and pulmonary embolism which often lead to death. Unfavorable allele of polymorphism (A) has autosomal dominant inheritance pattern. It means that the increased risk of thrombophilia might be even in case of heterozygotic form of polymorphism. S.R. Poort et al (1996) studied 418 persons of European origin with thrombosis aggravated family anamnesis. They found that allele A carriers have high risk of death during the postoperative period, as well as during cancer therapy and other diseases [28]. Symptoms of thrombophilia are shown at heterozygotic carriage, especially in case of combination with Leyden mutation. If the patient with chronic viral hepatitis has mutation of *FII (G20210A)* gene, the high speed of fibrosis can be explained both as formation of microblood clots in tissue of liver, and as effects of thrombin which is both the mitogen and the activator of star-shaped cells of liver.

In research of E. E. Starostina et al *FII* (*G20210A*) was found more often in group with "fast" fibrosis than in group with "slow" fibrosis [1].

A. Kallel et al (2016) studied 1290 people, and found that GG genotype is associated with high frequency myocardial infarctions among men [6].

In metaanalyse B. Jin et al (2011) did not find assosition between polymorphism of *FII (G20210A)* and the ischemic heart disease (IHD) among the Asian population, but they found out that polymorphism of *FII (G20210A)* increases risk of IHD among the European population [35]. In metaanalyse M. Dziadosz and L. V. Baxi found that SNP FII (G20210A) occurs among Asian population (in China, South Korea and Japan), however among aboriginals of the Middle East it is less than among Ashkenazi Jews (the frequency of this polymorphism is 2.5-12.25% and correlates with frequency of thromboses [11].

Results of this kind were obtained by S. K. Pandey et al (2012). They studied prevalence of *FII (G20210A)* among aboriginals of India with sickle-cell anaemia. However, this disease was associated with polymorphism of *G1691A* (rs6025) of *FV* gene – Leiden mutation [29].

In metaanalyse C. Li et al (2017) analysed 34 researches with participation of 14,611 patients with myocardial infarction (MI) and 84,358 healthy people. Statistically significant correlations between *FII (G20210A)* and MI was found during nucleotide replacement A>G. SNP of *FII (G20210A)* increases MI risk with the age. The metaanalyse showed that SNP of *FII (G20210A)* can represent risk factor for MI [31].

Thus, *FII (G20210A)* is not enough for formation of thrombophilia among Asian population and concedes on value to *FV (G1691A).*

***FVII* gene** encodes coagulation factor III which is a cell surface glycoprotein. This factor enables cells to initiate blood coagulation cascades, and it functions as a high-affinity receptor for the coagulation factor VII. This protein is the only thing in the way of coagulation which has no congenital disease.

***FV (G1691A)* (rs6025).** The *FV* gene provides instructions for making a protein called coagulation factor V. Coagulation factors are a group of related proteins that make up the coagulation system, a series of chemical reactions that form blood clots. The factor V protein is made primarily by cells in the liver. The protein circulates in the bloodstream in an inactive form until the coagulation system is activated by an injury that damages blood vessels. When coagulation factor V is activated, it interacts with coagulation factor X. The active forms of these two coagulation factors form a complex that converts an important coagulation protein called prothrombin to its active form, thrombin. Thrombin then converts a protein called fibrinogen into fibrin, which is the material that forms the clot.

The functional importance of genetic marker of *FV (G1691A)* was well described earlier. Inflammation in liver tissue at chronic hepatitises is associated with activation of coagulation system which is more expressed at patients with Leiden mutation and results in hyperactivity of thrombin and fibrin deposits. Thrombin is mitogen for liver star-shaped cells therefore start of coagulation cascade can stimulate star-shaped cells and fibrosis.

The metaanalyse of X. Shang et al (2013) revealed that Leiden mutation plays an important role in formation of an osteonecrosis of a femur, but not among Asian population [25].

In their research E. E. Starostina et al found that patients with fast rate of liver fibrosis more often have heterozygotic genotype *GA* of *FV* gene in comparison

with patients with slow rate of liver fibrosis [1].

In their research P. Angchaisuksiri et al (2000) found that the prevalence of SNP *FII (G20210A)* and *FV (G1691A)* is lower among Asians than among Caucasians. The low prevalence of these two mutations can explain the low frequency of thrombosis of deep veins in the Thai population [30].

In research of P.M. Ridker (USA, 1997) it was found that *FV (G1691A)* meets less often among the Asians living in the territory of the USA than among Caucasian Americans [14].

In research of A.A. Dashti et al (2011) it was found that Leiden mutation is present among the Iranian or Iraqi origin Kuwait citizens, and this mutation is not found among indigenous Arab Kuwait citizens [10].

De Stefano V. et al (1998) received similar results. They found that Leiden mutation is absent among Africans, Asians and races with Asian origin, such as Indians, Eskimos and Polynesians [12].

***FVII (G10976A*).** The *FVII* gene provides instructions for making a protein called coagulation factor VII. Coagulation factors are a group of related proteins that are involved in the coagulation system, which is a series of chemical reactions that form blood clots. After an injury, clots seal off blood vessels to stop bleeding and trigger blood vessel repair. Coagulation factor VII is made primarily by cells in the liver. The protein circulates in the bloodstream in an inactive form until the coagulation system is turned on (activated) by an injury that damages blood vessels. Activated coagulation factor VII helps to turn on other coagulation factors in turn. This step-wise process ultimately promotes the conversion of an important coagulation protein called fibrinogen into fibrin, which is the material that forms blood clots.

N.A. Zakai et al (2011) studied 815 cases of a stroke. SNP rs6046, rs3093261 (*FVII*); rs4918851, rs3781387 (*HABP2*); rs3138055 (*NFKB1A*); rs4648004 (*NFKB1*) related to ischemic stroke (p <0,01). SNP rs6046 and rs3093261 related to levels of VIIc factor. Ratios between SNP and ischemic stroke did not depend on levels of VIIc factor. The variation of genes related to VII factor, and levels of VIIc factor related to risk of ischemic stroke in elderly cohort, that indicates a potential causal role of VII factor in the etiology of ischemic stroke [7].

Minor alleles of SNP rs2146751, rs10665, rs1755685, rs6039 in *FVII* site reduce FVII level, and minor alleles rs964617 and rs762636 increase FVII level. SNP rs6046 leads to amino-acid replacement of Arg353Glu which reduces functional activity of protein of VII factor. Minor allele – *402A*, (rs510317) resulting from SNP *402GA* in FVII gene pro-motor increases activity of transcription. Rs510317 is associated with increased level of VIIc factor in plasma and increased risk of thromboses among Caucasian populations.

In metaanalyse X. Mo et al (2011) thirty-nine researches of SNP *FVII (R353Q)* (rs6046), *FVII (HVR4)* and *FVII (-323Ins10)* (rs36208070) were registered. The research of SNP *FVII (R353Q)* included 9151 cases of Coronary artery disease (CAD) and 14,099 people of control group, the research of SNP *FVII (HVR4)* included 2863 cases of CAD and 2727 people in control group, the research of SNP *FVII (-323Ins10)* included 2,862 cases and 4240 people in control group. Statistically significant association was found between *FVII (R353Q)* and CAD in Asian populations. Association for SNP *FVII (HVR4)* was not revealed [5].

Mutation of *F8, F9, F10, F11, F12* genes. Mutations in the *F8* gene cause hemophilia A, the most common form of bleeding disorder. More than 1,300 alterations of this gene have been identified. Some of these mutations change single DNA building blocks (base pairs) in the gene, while others delete or insert multiple base pairs. The most common mutation in people with severe hemophilia A is the rearrangement of genetic material called inversion. This inversion involves a large segment of the *F8* gene.

Mutations in the *F9* gene cause a type of hemophilia called hemophilia B. More than 900 alterations of this gene have been identified. The most common mutations change single DNA building blocks (base pairs) in the gene. Several rare mutations in the F9 gene cause an increased sensitivity (hypersensitivity) to a drug called warfarin.

Mutations in genes of X (*F10*), XI (*F11*), XII (*F12*) factors cause bleeding. However, it is not met very often. At least two mutations in the F12 gene are associated with hereditary angioedema type III.

SNP *G103T* (*F13A1*). The F13A1 gene provides instructions for making one part, the A subunit, of a protein called factor XIII. Factor XIII in the bloodstream is made of two A subunits (produced from the F13A1 gene) and two B subunits (produced from the F13B gene). When a new blood clot forms, the A and B subunits separate from one another, and the A subunit is cut (cleaved) to produce the active form of factor XIII (factor XIIIa). The active protein links together molecules of fibrin, the material that forms the clot, which strengthens the clot and keeps other molecules from breaking it down. Studies suggest that factor XIII has additional functions, although these are less understood than its role in blood clotting. Specifically, factor XIII is likely involved in other aspects of wound healing, immune system function, maintaining pregnancy, bone formation, and the growth of new blood vessels (angiogenesis).

At least 140 mutations in the *F13A1* gene have been found to cause inherited factor XIII deficiency, a rare bleeding disorder. Without treatment, affected individuals have a greatly increased risk of abnormal bleeding episodes, including life-threatening bleeding inside the skull (intracranial hemorrhage). *F13A1* gene mutations severely reduce the amount or activity of the A subunit of factor XIII. In most people with these mutations, the level of functional factor XIII in the bloodstream is less than 5 percent of normal. This loss of factor XIII activity weakens new blood clots and prevents them from stopping blood loss effectively.

The metaanalyse of Li J. et al (2015) included five researches: 382 cases and 352 controls. The prevalence of homozygous genotype of *Val/Val* of wild type was 64.9% (248 of 382) in group of patients and 75.9% (267 of 352) in control group. After the comprehensive analysis results showed that *F13A1 (Val34Leu)* is the link with thromboses, and women who had *Val/Val* genotype for *F13A1 (Val34Leu)* were not prone to abortions [18].

Mutation of *VWF gene*. The VWF gene provides instructions for making a blood clotting protein called von Willebrand factor. This protein contains regions that attach (bind) to specific cells and proteins during the formation of a blood clot. After an injury, clots protect the body by sealing off damaged blood vessels and preventing further blood loss. Cytogenetic Location: 12p13.31, which is the short (p) arm of chromosome 12 at position 13.31. Molecular Location: base pairs 5,948,874 to 6,124,675 on chromosome 12. More than 300 mutations in the VWF gene have been found to cause von Willebrand disease. It is deficient or defective in von Willebrand disease and is involved in a large number of other diseases, including thrombotic thrombocytopenic purpura, Heyde's syndrome, and possibly hemolytic-uremic syndrome.

Von Willebrand Factor's primary function is binding to other proteins, in particular factor VIII, and it is important in platelet adhesion to wound sites. It is not an enzyme and, thus, has no catalytic activity. VWF binds to a number of cells and molecules. Factor VIII is bound to

VWF while inactive in circulation; factor VIII degrades rapidly when not bound to VWF. Factor VIII is released from VWF by the action of thrombin. In the absence of VWF, factor VIII has a half-life of 1-2 hours; when carried by intact VWF, factor VIII has a half-life of 8-12 hours. VWF binds to collagen, e.g., when it is exposed in endothelial cells due to damage occurring to the blood vessel. Endothelium also releases VWF which forms additional links between the platelets' glycoprotein Ib/IX/V and the collagen fibrils. VWF binds to platelet gpIb when it forms a complex with gpIX and gpV; this binding occurs under all circumstances but is most efficient under high shear stress (i.e., rapid blood flow in narrow blood vessels, see below). VWF binds to other platelet receptors when they are activated, e.g., by thrombin (i.e., when coagulation has been stimulated).

W. Tang et al performed a genetic association study of *FVIIIc* and VWF that assessed 50,000 SNPs in 18,556 European Americans (EAs) and 5,047 African Americans (AAs) from five population-based cohorts. Previously unreported associations for *FVIIIc* were identified in both AAs and EAs with KNG1 (most significantly associated SNP rs710446, Ile581Thr, Ile581Thr, EAs and AAs). Significant associations for *FVIIIc* were also observed with rs12557310 in EAs, and with rs2236568 in AAs [16].

J. Song et al (2016) studied the connection of atherosclerosis and *ST3GAL4* as well as their connection with Willebrand's factor and VIII factor among 12117 subjects. 14 SNP of *ST3GAL4* rs2186717, rs7928391 and rs11220465 related to levels of Willebrand factor and with activity of VIII factor after adjustment on age, body mass index, hypertension, diabetes, smoking and blood group [8].

In many foreign researches it is established that homozygotes on minor allele of pro-motor SNP of VWF (3268GA) rs7966230 have higher Willebrand factor levels than homozygotes on widespread allele in population of healthy people. Minor allele of this SNP is associated with arterial thrombosis and with the increased risk of CAD among people with progressing atherosclerosis. Minor allele VWF (1793G) have carriers 2.6-fold, and carriers of WF (793GG) genotype – 3.5-fold increase in risk of CAD.

P.M. Ridker (1997) identified a number of SNPs participating in regulation of multimeasure *FV* size. When genotyping young patients with the first episode of an acute CAD or an ischemic stroke it was established that minor alleles of SNP rs4764478 (A/T), rs216293 (R/a) and rs1063857 (T2385C) were associated with substantial increase of the FV levels and risk of arterial thrombosis and cardiovascular diseases irrespective to other classical factors. SNP rs1063856 (*G2365A, Thr789Ala*) in the domain which participates in multimerization and linking with VIII factor is associated with FV level and risk of arterial thromboses. This association is revealed among healthy people and patients with CAD. SNP rs1063856 is associated with CAD risk among young patients with type 1 diabetes among Caucasian population. Euro-Americans have significant association between FV level and FVIII (Gly2705Arg) (rs7962217), because of disorders of FV multimeasure. This evidence points to the causal link between VWF and arterial thrombosis. Statistically significant correlations between *VWF* and CAD were found among high risk population [14].

SNP *5G (-675)4G* (*PAI-1).* Plasminogen activator inhibitor-1 (PAI-1) also known as endothelial plasminogen activator inhibitor or serpin E1 is a protein that is encoded by the SERPINE1 gene. Heterozygotic variant 5G (-675)4G prevails among population. Therefore, this SNP has no independent diagnostic value. Its effect is possible to estimate in combination with other factors contributing to development of pathology, for example, in combination with FGB (-467A). The allelic variant (-675)4G is followed by higher activity of gene, than *(-675)5G*, that causes higher concentration of *PAI-1* and reduction of fibrinolytic system activity. Homozygous *4G(-675)4G* is associated with increase in risk of thrombosis, pre-eclampsia, placenta disorders and spontaneous abortion.

In *SERPIN1* gene coding *PAI-1* SNP are identified: insertion/deletion of guanosine in position *4G(-675)5G (rs1799889), G(-844)A (rs2227631), c43GA (rs6092) and p.I17V (rs6090)* which change concentration of PAI-1 in plasma.

In the research of R. Natesirinilkul et al (2014) the level of PAI-1 and polymorphism 4G/5G among the Thai children did not show statistically significant interrelation with ischemic stroke. However, the mutation was found in 69-80% of the examined [22]. In the research of Li X. et al (2015) three variants (rs8093048, rs9946657, rs9320032) of PAI-2 gene were found in 407 patients with CAD and 518 people of the control groups of Chinese provinces of Han, and there was statistically significant with CAD [34].

K.N. Kim et al (2012) studied the link between SNP of PAI-1 of and hypertension among the Korean women and found correlation [32].

In the research of E. E. Starostina et al SNP of PAI-1 (5G (-675)4G) was more often detected among patients with "fast" fibrosis HCV-infection than among patients with "slow" fibrosis (55.62% against 47.16%) [1].

The interrelation between the speed of progressing of liver fibrosis among patients with HCV and polymorphic markers of other genes (MTHFR (C677T), FVII (G10976A), FXIII (C103T), GA2 (C807T), GB3 (T1565C)) is not revealed. Besides, Starostina et al found combinations of FII(GA)-FV(GG) and FII (GG)-FV(GA) meet more often in groups with "fast" fibrosis than in groups with "slow" fibrosis.

SNP T1565C (ITGB3). The ITGB3 gene provides instructions for making the beta3 subunit of a receptor protein called integrin alphaIIb/beta3 (αIIbβ3), which is found on the surface of small cell fragments called platelets. Platelets circulate in blood and are an essential component of blood clots. The beta3 subunit attaches (binds) to the alphaIIb subunit, which is produced from the ITGA2B gene, to form integrin αIIbβ3. It is estimated that 80,000 to 100,000 copies of integrin αIIbβ3 are present on the surface of each platelet.

Polymorphisms of the genes coding the proteins which are not entering the classical scheme of hemostasis. The results of GWAS which are carried out by Klarin D. at al (2017) demonstrate that the genes which are not link with coagulation can promote risk of venous thromboembolism (VTE). In metaanalyse researchers of INVENT Consortium gave the first instruction on the fact that genes out of coagulation cascade of TSPAN15 and SLC44A2 promote risk of VTE. In this research it was revealed that rs4602861 in ZFPM2 also promote risk of VTE. Multitype-2 protein is the known factor of transcription critical for hematopoiesis and development of heart. The locus is related with the circulating level of the growth factor of an endothelium of vessels (Vascular endothelial growth factor, VEGF), and recent data demonstrate that VEGF can be crucial for permission of venous blood clot. In total ZFPM2 can affect risk of VTE by means of modulation of the circulating VEGF and violation of balance of thrombosis in a venous system [17].

In meta-analyze which was carried out by K.C. Desch (2015), the following data were provided: the research found associations with alleles in genes of *F12, KNG1* among 1477 individuals (a gene of a kininogen 1) and HRG (histidine rich glycoprotein), all proteins were earlier described as a part of coagulative cascade. The subsequent larger research (9240 individuals) found additional signals in ABO, *FV*, and C6orf10 (an open frame of reading of chromosome 6), everything,

except C6orf10, had the known functions in the cascade of coagulation [24].

In GWAS-research Huang et al found associations for the activator of a fabric plasminogen (tPA) and inhibitor of the activator of plasminogen 1 (PAI-1) (more than 20000 individuals). The t-PA levels were statistically significantly connected with alleles of genes of two complex proteins of SNARE STX2 and STXBP5. These two loci were also connected with the FV levels [21].

In the research of M. Sabater-Lleal et al (2013) SNP rs4129267, rs6734238 and rs1154988 located in loci of IL6R, IL1F10/IL1RN and PCCB were considerably connected with fibrinogen level in blood and risk of development of cardiovascular diseases [26]. Q. Ma et al (2014) found significant associations with alleles in PLG locus (plasminogen) and LPA (apolipoprotein) and SIGLEC14 (sialic acid binding Ig like lectin 14) [20]. Also, in GWAS researches connection with disorders in hemostasis system and genes of PROCR was found (protein receptor C), EDEM2 (ER degradation-enhancing alpha-mannosidase-like protein 2), GCKR (regulatory protein of a glucokinase) and BAZ1B (Bromodomain Adjacent To Zinc Finger Domain 1B) [17].

Conclusion. All in all, common understanding of the influence of hemostasis genes polymorphism on chronic liver diseases is not yet been established. Pathophysiological and biochemical mechanisms of allelic variants impact of thrombophilia genes on progress and development of complications of this group of diseases, such as portal hypertensia, hepatocellular carcinoma, cryoglobulinemia, et al. are not well understood. While examining these issues the existence of other factors influencing rates of liver fibrosis (race, sex, age, virus genotype, presence of associated diseases, addictions, et al.) should be taken into consideration. Accordingly, a major concern has studying the influence of *FII G20210A* and *FV G1691A* which are not often found among population. A better understanding of the role of hemostasis genes' allelic variants in processes of intrahepatic epithelium is essential for prognosis of the impact the liver disease, as well as treatment and clinical background.

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GENETIC HETEROGENEITY OF PH-NEGATIVE CHRONIC MYELOPROLIFERATIVE DISEASES

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ABSTRACT

Chronic myeloproliferative diseases are clonal diseases of the hematopoietic system, characterized by uncontrolled proliferation of myeloid line cells. Classic Ph-negative chronic myeloproliferative diseases include polycythemia vera, essential thrombocythemia and primary myelofibrosis. Main complications that occur in patients with chronic MPD include thrombosis and transformation to secondary acute myeloid leukemia. A key factor of pathogenesis of this group of diseases is presented by activation of the JAK-STAT signaling pathway due to *JAK2* and *MPL* gene mutations, as well as mutation of *CALR* gene. These mutations play an important role in diagnosis and defining of disease prognosis and scoring possible complications. *JAK2*V617F mutation was demonstrated to be the most important risk factor for thrombosis, but did not have any affect in overall survival. *CALR*-positive patients with essential thrombocythemia and primary myelofibrosis have better prognosis than those with *JAK2* mutation. The worst prognosis has «triple-negative» patients with primary myelofibrosis.

Keywords: chronic myeloproliferative diseases, *JAK2, MPL, CALR.*

Introduction. Chronic myeloproliferative diseases (chronic MPD) include clonal diseases which originate from multipotent hematopoietic stem cell. Diseases pathogenesis is caused by excessive proliferation of one or more myeloid lineages (erythroid, megakaryocytic, granulocytic), differentiating into mature forms. Classical Ph-negative MPDs include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF).

PV is characterized by clonal stem cell proliferation of the erythroid, granulocytic, megakaryocytic lines, and splenomegaly [4]. In ET prominent proliferation of megakaryocytic line occurs [1]. Patients with PV and ET are usually asymptomatic over several years. Most commonly diseases manifest with symptoms of microcirculation disorders after a long period of latent increase in blood cells counts. Primary myelofibrosis (PMF) is characterized by bone marrow replacement with fibrous tissue, leading to development of cytopenia and extramedullary hematopoiesis, primarily in the spleen. Patients with PMF have the poorest prognosis among the patients with Ph-negative MPD. The average life expectancy of these patients is 5-7 years [3]. Patients with chronic MPD have a high risk of thrombohemorrhagic complications and disease progression with transformation to secondary acute myeloid leukemia (AML) [2].

Modern ideas about the pathogenesis of chronic MPD

Discovery of *JAK2* gene mutation in 2005 significantly improved understanding of Classical Ph-negative MPD pathogenesis. It was demonstrated that 1849 G/T point mutation in exon 14 of *JAK2* gene, leading to the substitution of valine for phenylalanine at position 617 of the nucleotide chain leads to an activation of the JAK2 tyrosine kinase gene product and uncontrolled proliferation of myeloid germ cells [10]. JAK2 is a non-receptor tyrosine kinase, which plays a key role in signal transduction from cytokines to receptors via the JAK-STAT signaling pathway. Seven homologous regions of the enzyme (JH) include domains - JH1, JH2, SH2 (JH3 and JH4) and FERM (JH6 and JH7) (Fig.). The JH1 domain, an active kinase domain, located at the C-terminus (carboxyl) of protein, while the JH2 (pseudokinase) domain is considered to be catalytically inactive region. Pseudokinase domain inhibits the JH1 domain causes inhibition of JAK2 activity. The FERM and SH2 domains provide for the binding of JAK kinase and transmembrane cytokine receptors and regulate the kinase activity of the enzyme. When tyrosine kinase is affected by cytokine ligands (erythropoietin, thrombopoietin, interleukins), tyrosine is phosphorylated at the end of the JH1 domain, which causes signal transmission through the STAT5 proteins, STAT3, PAS-MARK and PI3K-AKT. The V617F mutation, located on the JH2 regulatory domain, results in the loss of autoinhibitory properties of JAK2 tyrosine kinase, its hyperactivation and cytokine-independent differentiation of myeloid cells [5, 6, 14]. In most cases, among patients with PV and PMF *JAK2*V617F, the mutation occurs in homozygous state with an allele burden of more than 50%. In these patients, as a result of mitotic recombination of chromosome 9p and duplication of mutant allele, the heterozygous mutation *JAK2*V617F transforms to the homozygous form. Among patients with ET heterozygous form of mutation with an allelic load of less than 50% is commonly observed [17].

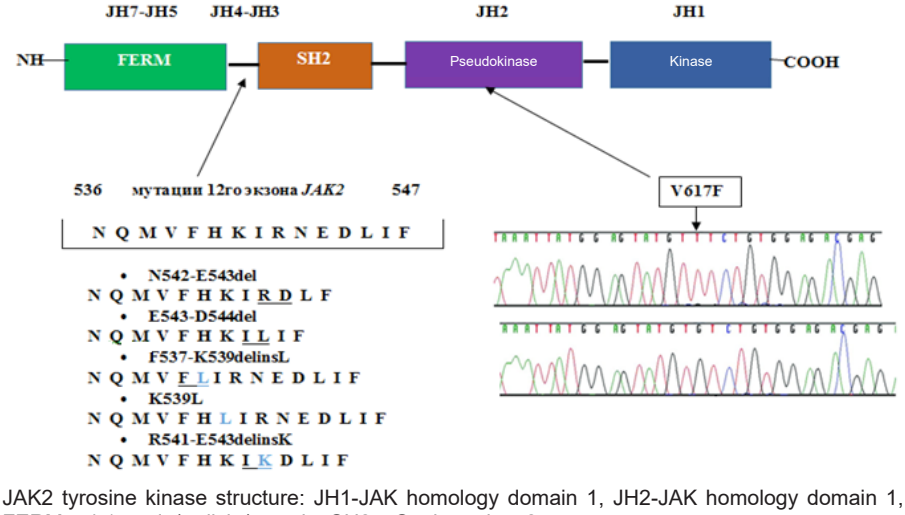
The second clinically significant mutation of *JAK2* gene is 12 exon mutation, which includes more than 40 different mutations located between the pseudokinase and SH2 domains (Fig.). The most common of these include mutations N542-E543del (23%), E543-D544del (11%), F537-K539delinsL and K539L (10%), and R541-E543delinsK (8%) [12, 24]. By changing the structure of the JH2 domain, they lead to a modification of the response to growth factor [2].

In the pathogenesis of megakaryocyte line proliferation, mutations in the *MPL* and *CALR* genes play a leading role. The *MPL* gene (myeloproliferative leukaemia virus) is located on chromosome 1p34, encodes a thrombopoietin receptor and is a key factor in the proliferation and differentiation of megakaryocytes. Clinical importance have mutations in 515 position of the *MPL*: W515L mutation (replacement of tryptophan with leucine at position 515) and W515K (replacement of tryptophan with lysine) [20]. Tryptophan at position 515 (W515) is a part of transmembrane domain, normally support the thromboprotein receptor in an inactive state, inhibiting its dimerization [29] .W515L/K mutations lead to spontaneous activation of the MPL receptor, increasing its sensitivity to thrombopoietin and cytokine-independent proliferation of hematopoietic cells.

The *CALR* gene (calreticulin) is located on the short arm of chromosome 19 (19p13.2). Calreticulin is a multifunctional protein expressed in the endoplasmic reticulum, cytoplasm, cell surface, extracellular matrix. Its main role is to keep calcium homeostasis, and also participates in the processes of proliferation, apoptosis, phagocytosis and the immune response [28]. To date, two mutations of exon 9 of *CALR* have been described, which plays an important role in the development of chronic MPD — a type 1 mutation (p.L367fs*46), representing a 52 b.p. deletion and mutation type 2 (p.K385fs*47) is an insertion of TTGTC. *CALR* mutations lead to a shift in the reading frame, the formation of a new C-terminal protein sequence and the loss of the KDEL signal sequence [3].

The prevalence of *JAK2*V617F mutation among patients with PV is more than 95%, and mutation of exon 12 – 4%. Among patients with ET and PMF, *JAK2*V617F mutation is detected in 60% of cases. Among patients with ET and PMF, *CALR* mutations are detected in 20-25% of cases, MPL is detected in 5%, and no mutations are detected in 5-10% [26].

Mutations of the *JAK2*, *MPL* and *CALR* genes are drivers that activate the JAK2 signaling pathway. In addition to the main driver mutations, a number of somatic mutations (in genes *TET2, ASXL1, DNMT3A, CBL, LNK, IDH1*



JAK2 tyrosine kinase structure: JH1-JAK homology domain 1, JH2-JAK homology domain 1, FERM – 4.1, ezrin/radixin/moesin, SH2 – Src homology2

/ 2, IKF1, EZH2, TP53, SRSF2) are described, encoding transcriptional and epigenetic factors. The role of these mutations, according to some authors, is to modulate the activity of the disease [26].

Hereditary predisposition to the development of chronic MPDs

Despite the fact that chronic MPDs are triggered by somatic mutations, family cases of this group of diseases are described [11]. The search of correlations between driver somatic mutations and different single nucleotide polymorphisms (SNPs) in the four candidate genes (EPOR, MPL, GCSFR and JAK2) by different groups of scientists led to the discovery of a link between the presence of specific SNPs *JAK2* gene and the development of chronic MPDs [17]. As a result of the conducted research, it was proved that hereditary predisposition to chronic MPDs is caused by carrying the haplotype 46/1 of *JAK2* gene. It is represented by 4 main SNPs (rs3780367, rs10974944, rs12343867 and rs1159782), which lead to the replacement of three thymidine residues (T) and one cytosine (C) with two guanosine (G) and two cytosine (C), forming a combination of “GGCC” [28].

The prevalence of *JAK2* 46/1 haplotype in a healthy population is about 24%, compared to 40–80% and 64% in *JAK2*V617F and 12 exon mutated patients with chronic MPDs. The potential link between the GGCC_46/1 haplotype and the somatic *JAK2* mutations is explained by the hypothesis of “hypermutability”, according to which the haplotype can somehow stimulate the mutation frequency in the *JAK2* gene [28].

Mutational status and disease phenotype

The determination of allele burden of the *JAK2*V617F mutation has a great importance in predicting the development of complications and outcomes of chronic MPD. Many studies have shown that the higher the allele burden cause more aggressive source of disease with high blood counts, massive splenomegaly and high risk of thrombotic complications [2].

The level of allele burden *JAK2*V617F is higher in patients with PV, compared with patients with ET and PMF [13]. *JAK2*V617F-positive patients with PV are more often characterized by three-lineage proliferation, when patients with 12 exon mutation of *JAK2* demonstrate a high level of hemoglobin, relatively low levels of platelets and leukocytes. In general, isolated erythrocytosis in PV, especially in young people, is a characteristic for *JAK2* exon 12 mutation [2].

In ET, *JAK2*V617F-positivity is characterized by clinics similar to PMF — a high level of hemoglobin, a relatively mild thrombocytosis [29], and a high rate of progression to PV [16]. Mutation of the *CALR* gene in patients with ET is associated with hyperthrombocytosis (> $1000*10^9$), but the risk of thrombotic complications is lower than in patients with the mutation *JAK2*V617F [7]. When comparing groups of patients with PV and ET and *JAK2*V617F mutation, the frequency of thrombosis did not differ, which suggests that the V617F mutation of the *JAK2* gene is the main marker of thrombogenic risk [28]. The high prevalence of thrombosis among JAK2-positive patients with ET is associated with hyperviscosity syndrome due to increased hematocrit and leukocytosis. The role of *MPL* mutation in patients with ET is not fully understood. According to some authors, the presence of *MPL* gene mutation is associated with a high frequency of transformation to secondary myelofibrosis and low survival rates [21, 22].

Patients with PMF with the *JAK2*V617F mutation have massive splenomegaly, high leukocytosis, thrombocytosis, low hemoglobin levels, which are unfavorable factors for the development of blast crisis and low overall survival rates [2]. *CALR*-positive patients with PMF usually have young age, low leukocyte count, and high thrombocytosis. During long-term follow-up of patients with *CALR* mutation, it was demonstrated that, compared with other mutational groups, they have a lower cumulative risk of developing anemia, thrombocytopenia, leukocytosis more than $25x10^9$/l and a longer interval of development of massive splenomegaly. The risk of thrombosis and blast transformation is also lower in patients with *CALR* mutation [11].

Mutational status and prognosis of the disease

ET and PV are diseases with a relatively benign course (average survival is 19,8 and 13,5 years, respectively), when PMF is characterized by low average survival rates (5,9 years), high risk of blast transformation and associated mortality [18].

The mutational status of *JAK2* does not affect the disease outcome. Clinical studies have demonstrated that the incidence of thrombotic complications, the development of secondary myelofibrosis, acute leukemia and death does not differ between patients with *JAK2*V617F and exon 12 mutations [19]. However, patients with a high allele burden are more likely to have thrombosis and transformation to myelofibrosis [25]. Allele burden did not demonstrate any affect to patients survival [15].

Among patients with ET, patients with *CALR* mutation have a more favorable prognosis compared with patients with *JAK2* mutation [1]. For *CALR*-positive patients, the best response to interferon therapy was demonstrated, and for *MPL*-positive patients, according to some authors, there is a high incidence of transformation to postthrombocythemic fibrosis [18] and low overall survival rates [22].

In case of PMF, the presence of a *CALR* mutation is also associated with a favorable prognosis of the disease with late development of anemia, leukocytosis, massive splenomegaly and low incidence of thrombosis (average overall survival of 17,7 years, cumulative 10-year risk of blast transformation 9,4%). *JAK2*-positive patients with PMF more frequently develop thrombotic complications, as in the case of PV and ET. The worst prognosis have patients with “triple negativity”, for whom the risk of blast transformation is 34%, and the average overall survival is 3.2 years [25].

Conclusion. The discovery of mutations in *JAK2*, *MPL* and *CALR* genes radically changed the understanding of the pathogenesis of Ph-negative chronic MPD. The introduction into clinical practice of various methods of molecular genetic research has improved the diagnosis of diseases, contributed to the development of prognostic scales and a personalized approach to therapy. Because of diversity of chronic MPDs phenotypes, due to genetic heterogeneity, practicians need molecular genetic tests to identify driver mutations and determine the prognosis, the risk of complications and the choice of patient management approach. However, more research is needed to clarify the role of other molecular events in the pathogenesis and formation of the phenotype of diseases.

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BROWN ADIPOSE TISSUE: MAIN STAGES OF RESEARCH AND POTENTIAL ROLE IN ENERGY BALANCE AND OBESITY

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ABSTRACT

Obesity and diabetes mellitus are worldwide epidemics driven by the disruption in energy balance. In recent years, it was discovered that functional brown adipose tissue (BAT), once thought to exist mainly in infants, is present in adults, and can be detected during cold stimulation, and is associated with decreased adiposity. Brown fat pads were shown to be highly vascularized and metabolically active and on stimulation, they caused enhanced energy expenditure and increased glucose and fatty acid uptake. These observations drew attention to the possibility that nonshivering thermogenesis medited by activation of BAT might be important in human energy balance and a potential tool to counter obesity. Recent investigations have revealed significant advances in the understanding of the role of BAT-mediated thermogenesis, uncovering essential knowledge on the origin, differentiation, activation, and regulation of BAT in both murine models and humans. In addition to classic BAT depots, transformation of white adipocytes into brown-like adipocytes, and the development of “beige” cells from distinct precursors, were demonstrated in different animal models and resulted in increased thermogenic activity. This review will summarize the evolution of research on BAT in humans, in light of the renewed scientific interest and growing body of evidence showing that recruitment and activation of BAT and browning of white adipose tis- sue can affect energy expenditure and may be a future feasible target in the treatment of metabolic diseases.

Keywords: brown adipose tissue, obesity, energy balance, UCP1.

Introduction. Obesity is a major public health problem and a global epidemic that contributes to the development of dyslipidymia, type 2 diabetes and cardiovascular diseases [42]. Treating patients with obesity requires serious efforts in lifestyle changes. Other methods, such as medication and bariatric surgery, are only suitable for a limited group of people. Therefore, a significant effort is aimed at developing the latest therapeutic tools to combat obesity. One possible solution would be to increase energy consumption through the activation of brown adipose tissue.

Brown adipose tissue (BAT) is a unique adipose tissue, its main function is to generate heat by dissipating chemical energy. Until recently, it was believed that among people BAT is present only in newborns [4]. However, at present there is a belief that BAT is also active in adults and can be a therapeutic way against obesity. An obstacle to achieving these goals is the small number of BAT in adults, especially in older people.

The purpose of this article is to review the topics of current research on BAT and its impact on energy balance, obesity and metabolic diseases.

The epidemic of obesity and energy balance. According to the WHO, the number of people with obesity has increased by more than 2 times worldwide, including among children [11, 32, 42]. Currently, obesity is the main cause of pathologies, disability, premature mortality [2].

Obesity is a frequent result of an imbalance between energy intake and consumption, which consists of a basal metabolic level and physical work, which includes physical activity and non-physical adaptive thermogenesis [14, 25]. The main factors contributing to the imbalance are a decrease in physical activity with an increase in the energy consumption of high-calorie foods and drinks [6]. An important factor that can play a role in the energy balance and the development of obesity is the temperature of the environment [15].

However, it is not easy to influence the energy balance by intensive lifestyle changes in people with obesity. Caloric restriction is accompanied by unpleasant sensations of hunger and compensation, leading to a decrease in the basal metabolic rate and a decrease in physical activity [22, 35].Due to the limited efficacy of drugs, bariatric surgery has improved significantly in recent years. It has been shown to improve metabolic dysfunction, reduce the levels of inflammatory cytokines [12], and help improve glycemic control in patients with obesity and diabetes [21]. However, these procedures are invasive, have potential complications and are a therapeutic option for a small number of patients with severe obesity and concomitant diseases. Therefore, methods to increase energy costs are still needed for obese patients. For example, the use of BAT features, a unique feature of which is to stimulate lipid metabolism to activate thermogenesis, which thus increases energy consumption.

BAT consists of brown adipocytes, characterized by a large number of mitochondria. BAT mitochondria are unique in expressing the release of protein 1 (UCP1) in the inner mitochondrial membrane. When activated, this protein separates the electron transfer in the respiratory chain from the formation of adenosine triphosphate and, thus, converts chemical energy, which mainly originates from fatty acids, into thermal energy, leading to thermogenesis. It should be emphasized that UCP1 is present only in BAT and is not characteristic of white adipose tissue. BAT is physiologically active in newborns. Its evolutionary function is to generate heat when no other means of producing it has been developed. After puberty, the number and activity of BAT decreases rapidly. However, in adults, BAT is found in the supraclavicular and cervical areas, around the spinal cord and the paravertebral and periaortic areas.

Study of brown adipose tissue in adults. For the first time, physiologically active BAT in humans was described several decades ago, and the question of the clinical significance of BAT in adults was raised in the 1970s [29, 37]. In 1981, it was stated that working in the cold could contribute to the activation and increase in the mass of BAT [37]. Several studies have shown that catecholamines stimulate BAT thermogenesis and negatively correlate with obesity [17, 18].However, until recent years, BAT was considered a tissue without significant physiological significance in healthy adults. Scientific interest in the physiology of brown adipose tissue occurred in the 1990s — during FDG-PET scans, physiologically active BAT were found in the upper surface of the neck [26]. In 2002, Hani and colleagues found that BAT probably increased under the influence of cold stress on sympathetic activity [13]. A few years later, Nedergaard and colleagues put forward “unexpected evidence of BAT activity in adults,” its potential in human metabolism and physiology, and a possible role in the fight against obesity [31].Until recently, the results of FDG-PET showed the presence of active BAT only in a small proportion of adults. So, in 2009, Cypress et al. demonstrated

the presence of BAT depot in the front of the neck and chest in 7.5% of women and 3% of men (without stimulating the activity of BIT) [7]. However, the scientific team Lichtenbelt found active BAT in 23 of 24 healthy men during mild exposure to cold. This activity has a negative correlation with BMI, supporting the possibility of applying regulation of BAT activity in people with obesity [38]. Saito's research also demonstrated cold-induced FDG-PET / CT in 27 of 32 healthy young volunteers [36].All these studies prove the presence of BAT in a more significant proportion of adults than in earlier studies that were carried out in thermoneutral conditions.The next step was to confirm that BAT is actually metabolically active in humans and contributes to cold-induced non-contractile thermogenesis. A number of studies have shown that cold activates BAT more than 2 times, increasing the rate of perfusion in tissue, which is associated with energy metabolism during cold exposure and confirms active thermogenesis [8, 43]. The scientific group Qellet found that cold activation of BAT is also associated with high oxidative metabolism in the tissue. Researchers have shown an increase in the consumption of triglycerides as energy sources during BAT thermogenesis [34].

However, another study shows that despite the high glucose uptake in BAT, active BAT does not significantly contribute to energy expenditure [33]. Low activity of BAT depot may reflect low density of brown adipocytes - therefore, to increase energy expenditure, their excess will be needed.BAT and human interactions

The main question is whether the presence, mass or activity of BAT affects the development of obesity. It is preliminary shown that we are dealing with an increase in body weight; overexpression of transgenic mice with UCP1 protection against obesity; and adrenergic stimulation of β3-adrenergic receptors, leading to the appearance of brown adipocytes in white tissue, accompanied by increased expression of UCP1 and a decrease in body weight [36, 38, 45].Recent studies have shown a negative correlation between BAT activity and various obesity parameters, such as BMI, fat percentage and fat composition [9,13, 33, 39, 41]. After weight loss by bariarthric surgery, a significantly high non-contractile thermogenesis was observed in BAT-positive patients compared with BAT negative group [44].

Other clinical correlations

At present, a clear decrease in the activity of BAT, which is associated with the age of the subjects [5, 13, 30, 33, 34], has been proven. Several studies have shown that BAT predominates more in women than in men [5,27,30,41].

The relationship between the detection of BAT and ambient temperature is also well understood. Activation of BAT was most often recorded during the cold season [27], and seasonal variations, the external temperature, apparently, are associated with the presence of BAT [13, 28.41]. In the work of Hyuang Y.C, it was shown that the prevalence of active BAT decreases by 1% with each increase in the external environment by 5 ° C, and the prevalence of BAT is rarely found in tropical zones [46].

Conclusion. Recent studies suggest that BAT-mediated thermogenesis may play a major role in the energy balance. Activation of BAT can have therapeutic potential in treating patients with obesity, diabetes and metabolic syndrome, providing new treatment options.

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TREATMENT OF CHILDREN WITH OSTEOSARCOMA

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ABSTRACT

Osteosarcoma accounts for 3% of all malignant tumors, 35-50% of all malignant bone tumors in pediatric patients. The paper contains statistical data describing the incidence of the child population of osteosarcomas, classification of osteosarcomas, staging principles, a description of the main localizations, as well as a detailed description of the existing treatment protocols for children with osteosarcomas, including personalized therapy.

The literature data are described in detail - the results of treatment of children with osteosarcoma with various courses of chemotherapy, as well as new approaches in treatment, including personalized therapy. But the results of treatment of children with primary metastatic osteosarcoma, relapse and refractory course of the disease remain unsatisfactory.

Molecular biological factors that determine sensitivity to chemotherapy, invasive and metastatic potential of the tumor, as well as the prognosis of the disease, among which special attention is deserved: expression of MGMT protein, methylation of the promoter part of the MGMT gene, expression of ERCC1 proteins, VEGF, CD133, p -STAT3tyr705, C-MYC, expression of RFC1 micro-RNA and the presence of rearrangement of the TOR2A gene. It is important to note the following fact that there was no comprehensive assessment of the value of these markers for the histological response to neoadjuvant chemotherapy and survival rates in patients with osteosarcoma.

Keywords: pediatric oncology, osteosarcoma, chemotherapy, personalized therapy, combination treatment.

Introduction. Osteosarcoma is a primary malignant bone tumor that develops from primitive mesenchymal stem cells capable of differentiating into bone, cartilage or fibrous tissue [20].

Osteosarcoma accounts for 3% of all malignant tumors, 35-50% of all malignant bone tumors in pediatric patients. The frequency of occurrence is 4 cases per 1 million children and adolescents per year. About 60% of cases of osteosarcoma detection are recorded at the age of 10 to 20 years (mainly in the prepubertal and pubertal periods). The gender ratio (boys / girls) is 1.3-1.6: 1 35].

In 50% of cases, the tumor is located in the projection of the knee joint (distal femur, proximal tibial bone). The third place in terms of frequency of occurrence is the lesion of the proximal metadiaphysis of the humerus. The defeat of the axial skeleton (pelvis, spinal column) is detected in 12% of cases [20, 35].

Classification and staging

WHO classification of soft tissue and bone tumors of 2013 (fourth revision) [10].

A localized (locally advanced) variant of osteosarcoma, which occurs in 80% of cases, and a disseminated (primary metastatic) variant, which occurs in 20% of cases, are distinguished.

Histological classification of osteosarcomas:

- low grade, central;
- classic (conventional) version:
- chondroblastic;
- fibroblastic;
- osteoblastic;
- unspecified accuracy;
- telangiectatic;
- small cell;
- high degree of malignancy, superficial.

Staging according to the TNM classification is presented in Table 1.

Table 1

Staging by TNM

Stage	TNM	Degree of malignancy
IA	T1 N0 M0	low
IB	T2 N0 M0	low
IIA	T1 N0 M0	high
IIB	T2 N0 M0	high
III	T3 N0 M0	any
IVA	Any T N0 M1a	any
IVB	Any T N1 Any МЛюбое Any T Any N M1b	any any

Treatment. The methods of treatment of osteosarcoma over the past thirty years have not changed. There are five main drugs (cisplatin, adriamycin, methotrexate, ifosfamide, etoposide), which were used in various combinations and doses [1]. The rates of treatment outcome in the world remain approximately the same. In patients with a localized variant of osteosarcoma, 5-year overall survival (OS) does not exceed 75%, 5-year event-free survival (BSV) - 62% (Table 1).

In patients with primary metastatic osteosarcoma, the results are much worse, despite attempts to use high doses of drugs, including high-dose polychemotherapy with transplantation of autologous hematopoietic stem cells. At the same time, the 5-year OM does not exceed 35% on average, the 5-year BSV — 25% (Table 2).

The most significant interest in treating children with a localized osteosarcoma is the study of the Italian and Scandinavian groups (Italian and

Table 2

The results of the treatment of pediatric patients with localized osteosarcoma

Therapy program	5-year overall survival, %	5-year event-free survival, %
IOR/OS2 the Istituto Ortopedico Rizzoli [2]	75	63
ISG/OS1 (Italian Sarcoma Group) [8]	74	64
ISG/SSG1 (Italian and Scandinavian Sarcoma Group) [9]	77	64
COSS 88/96 (Cooperative Osteosarcoma Study Group) [17]	79	
SSG XIV (Scandinavian Sarcoma Group) [31]		65
NECO93J/95J (Neoadjuvant Chemotherapy for Osteosarcoma) [21]	78	65
BOTG III/IV (Brazilian Osteosarcoma Treatment Group) [28]	61	45
POG8651 (Pediatric Oncology Group) [11]	78	65
SFOP94 (Société Française d'Oncologie Pédiatrique) [22]	76	62
St.Jude CRH OS91 (Children Research Hospital) [18]	74	65
St.Jude CRH OS99 (Children Research Hospital) [5]	79	67
INT0133-COG (+MTP/-MTP) Children's Oncology Group [26]	78/70	67/61
MSKC NY (+PAM) Memorial Sloan-Kettering Cancer Center, NY [25]	94	72
COG INT0133, CCG7943, AOST0121 [25]	47	22
ISG/SSG II (Italian and Scandinavian Sarcoma Group) [26]	55	46
EURAMOS1 [30]	75	59

Scandinavian sarcoma group - ISG / SSGI, SSG XIV), the French Pediatric Oncological Group (Societe Francaise d'Oncologie Pediatricue - SFOP OS94), and EURAMOS1.

Ferrari S. et al. showed the data of the joint study of the Italian and Scandinavian groups (ISG / SSG I), which was conducted from 1997 to 2000. The study included 182 patients. A special feature of neoadjuvant chemotherapy was the use of two courses of monotherapy with high-dose ifosfamide (in a course dose of 15 g / m2) and two courses of MAR (methotrexate (M) 12 g / m2, adriamycin (A) 75 mg / m2, cisplatin (P) 120 mg / m2) in alternating mode. Adjuvant chemotherapy started at week 14. The course dose of adriamycin was increased to 90 mg / m2, the dose of cisplatin to 150 mg / m2, high-dose ifosfamide was administered in PIM chemotherapy courses (cisplatin, ifosfamide, methotrexate) and PAI (cisplatin, adriamycin, ifosfamide).

After removal of the primary tumor focus, a good histological response (therapeutic pathomorphism of grade 3–4) was achieved in 63% of patients, a poor histological response (treatment pathomorphism of grade 1–2) in 37%. At the same time, the 5-year OV and BSV accounted for 77% and 64%. Consequently, the use of high-dose ifosfamide in an alternating mode with the IDA scheme led to an increase in the frequency of achieving a good histological response, but did not affect the rates of OS and BSV [8, 9].

Smeland S. et al. presented the data of the study of the Scandinavian Group (SSG XIV), which was conducted from 2001 to 2005. The study included 63 patients. Neoadjuvant chemotherapy consisted of 2 courses of IDA. High-dose ifosfamide (in a course dose of 10 g / m2) was used in monotherapy in patients with a poor histological response to treatment, only after 5 courses of MAP.

After removal of the primary tumor lesion, a good histological response was achieved in 45% of patients, a poor histological response in 55%. At the same time, the 5-year OV and BSV accounted for 76% and 65%, the 5-year BSV in the group with a good histological response - 89%, with a poor histological response - 48%. Consequently, the use of ifosfamide after MAP courses in the adjuvant mode did not lead to an increase in OS and BSV, and the frequency of achieving a good histological response was lower than in studies in which the MAP scheme was used in an alternating mode with ifosfamide [31].

Le Deley M.C. et al. presented the results of the randomized SFOP OS94 study, which was conducted from 1994 to 2001. The study included 239 patients (120 in group A, 119 in group B).

Neoadjuvant therapy included 7 courses of high-dose methotrexate and 2 courses of monotherapy with adriamycin (in a course dose of 70 mg / m2) in group A or 7 courses of high-dose methotrexate and 2 courses of IE (ifosfamide (I) 12 g / m2, etoposide (E) 300 mg / m2) in group B. In the adjuvant mode, chemotherapy was replaced with IE courses in group A, and AR in group B for patients with a poor histological response, detected after removal of the primary focus. The operative stage of treatment was carried out at 12 and 14 weeks in groups A and B, respectively.

A good histological response was achieved in group A in 43% of patients, in group B in 64%, poor histological response in group A in 57%, in group B in 36% (p = 0.009). The 5-year OM in Group A was 75%, in the Group B - 76%, the 5-year BSV in Group A - 58%, in Group B - 66%. 3-year BSV in group A in patients with a good histological response - 82%, with a poor histological response - 49%, in group B - 77% and 60%, respectively. Consequently, the use of methotrexate, ifosfamide, etoposide in neoadjuvant chemotherapy led to a statistically significant increase in the frequency of achieving a good histological response, but not to an increase in OS and BSV [22]. Of particular interest in the treatment of children with primary metastatic osteosarcoma are the POG IE (Pediatric Oncology group) and ISG / SSG II studies. Goorin A.M. et al. presented the results of a phase II / III non-randomized clinical trial of high-dose ifosfamide and etoposide in patients with primary metastatic osteosarcoma. The study included 43 patients.

Neoadjuvant chemotherapy was represented by 2 courses of IE (ifosfamide (I) 17.5 g / m2, etoposide (E) 500 mg / m2). Removal of the primary tumor lesion was performed after 2 courses of IE at 7-8 weeks of therapy. The timing of the removal of metastatic foci was chosen individually during adjuvant chemotherapy, which included 4 courses of MAP chemotherapy and 3 courses of iE (with a course dose of ifosfamide (i) 12 g / m2) in an alternating mode. A good histological response was achieved in 65% of patients, poor in 35%. However, the 2-year-old RH and BSV were 55% and 45%. Consequently, the use of high-dose ifosfamide in combination with etoposide therapy led to an increase in the frequency of achieving a good histological response, but not indicators of OS and BSV [12].

Boye K. et al. showed the results of the non-randomized study ISG / SSG II, which was conducted from 1996 to 2004. The study included 57 patients with primary metastatic osteosarcoma.

Neoadjuvant chemotherapy included 2 courses of MAPI. Surgical removal of the primary tumor lesion was performed at week 14.

In the adjuvant regimen, 2 courses of ACyVP (adriamycin (A) 90 mg / m2, cyclophosphamide (Cy) 4 g / m2, vepezid (VP) 600 mg / m2) and 2 courses of high-dose chemotherapy VPCarbo (vepezid (VP) 600 mg / m2 , carboplatin (Carbo) 1.5 g / m2) with the support of autologous hematopoietic stem cells. Surgical removal of the primary tumor lesion was performed at week 14.

A good histological response was achieved in 29% of patients, poor in 71%. The 5-year OM and BSV were 31% and 27% [3].

Marina N.M. et al. presented the results of the EURAMOS1 study in patients with a poor histological response after neoadjuvant MAP chemotherapy. Within the protocol, patients are randomly assigned to the MAP treatment lines (methotrexate (M) 12 g / m2, adriamycin (A) 75 mg / m2, cisplatin (P) 120 mg / m2) and MAPIE (ifosfamide (I) 14 g / m2, etoposide 500 mg / m2). In the age group up to 30 years, the MAPIE line of therapy was carried out in 310 patients, the MAPIE line in 308 patients, in the age group up to 20 years - 259 (84%) and 271 (88%) patients. Groups of patients are statistically significantly comparable by gender, age, localization of the primary tumor lesion, the presence of a metastatic lesion, the histological variant of the tumor.

In the group of 541 patients with a localized version of osteosarcoma, 247 events were identified, 118 in patients who received the MAP therapy line, 129 in patients who received the MAPIE therapy line. At the same time, the 3-year BSV was 60% and 57%. In the group of patients with primary metastatic osteosarcoma, 3-year BSV was 24% and 18%, for MAP and MAPIE, respectively. Consequently, this study showed that the use of alternating chemotherapy courses for MAP, IE, and Ai in an adjuvant regimen did not lead to an increase in BSV rates [24].

Treatment outcomes for children with primary metastatic osteosarcoma remain extremely low and the optimal therapeutic strategy is unknown. New programs are being developed around the world taking into account the molecular biological features of

tumor cells that determine sensitivity to chemotherapy (ERCC1 to cisplatin, TOPO2α to anthracyclines and etoposide, MGMT to epigenetic therapy and cisplatin, RFC1 to methotrexate) [4], invasive and metastatic potential of the tumor (stem cell markers - CD133, OCT4; transcription factors - p-STAT3, C-MYC; cytokine-associated signaling pathways - ErbB2, VEGFR1, VEGFR2, PDGFRα, PDGFRβ) [13]. Cui Q. et al. presented the results of a study to determine the expression of MGMT protein (methylguanine - DNA - methyltransferase) and MGMT gene methylation in patients with osteosarcoma in the age group up to 40 years (mean age 17 years) who were treated with cisplatin in single mode, in a course dose of 120 mg / m2. Determination of MGMT protein expression in immunohistochemical (IHC) study was performed in biopsy tumor material in 76 patients, MGMT gene methylation in 51 patients. The result of IHC was considered positive with a high expression level — more than 30% (3+), with an average expression level — 20-30% (2+), with a low expression level — 10-20% (1+). MGMT protein expression was detected in 52 (68%) patients, low expression level in 27 (35%), medium level in 18 (24%), high level in 7 (9%).

A statistically significant relationship was established between the presence of MGMT protein expression and an increase in the frequency of a poor histological response (p = 0.004). The expression level above 20% was detected in 22 out of 43 (51%) patients in the group of patients with 1–2 degrees of therapeutic pathomorphosis and only in 3 out of 33 (9%) patients in the group with 3–4 degrees of therapeutic pathomorphosis. Methylation of the promoter portion of the MGMT gene was observed in 12 of 51 (23.5%) patients, and the lack of expression of MGMT protein in 14 of 51 (27.5%) patients. A statistically significant relationship between the absence of methylation and the presence of MGMT protein expression (p <0.001) was established. In the group of patients with 1–2 degrees of therapeutic pathomorphosis, the absence of MGMT gene methylation was detected in 36 of 38 (94.7%) patients, and with 3–4 degrees of therapeutic pathomorphosis in 3 of 13 (23%) patients (p <0.001).

Consequently, the data obtained indicate the formation of tumor resistance to treatment with an alkylating agent — cisplatin in patients whose biopsy material revealed no methylation of the promoter portion of the MGMT gene and the presence of MGMT protein expression [4]. Pitano-Garcia A. et al. (Spain sarcoma group) conducted a study to determine the expression of RFC1 micro-RNA (reduced folate carrier 1, a transmembrane protein that provides folate and methotrexate transport to the cell) by real-time polymerase chain reaction (PCR) in a tumor substrate in children with osteosarcoma.

The analysis of 34 samples, biopsy tumor material in 14 children, tumor material metastatic foci in 20 children. In 13 of 14 (92.9%) biopsy specimens, in 11 of 20 (68.8%) metastatic specimens, a low level of RFC1 expression was detected.

A poor histological response after neoadjuvant chemotherapy (3 courses of intravenous doxorubicin at a dose of 75 mg / m2, 3 courses of intra-arterial administration of cisplatin at a dose of 105 mg / m2, 4 courses of intravenous methotrexate at a dose of 14 g / m2) was set up in 45% of cases. The biopsy tumor substrate in this group of patients was characterized by a low level of expression of RFC1 micro-RNA in 90% of cases compared to 60% in patients with a good histological response (p = 0.053). The average level of expression was statistically significantly lower in the biopsy material than in metastatic tumor foci (p = 0.024) [29]. Consequently, in this study, there was a tendency to an increase in the frequency of detecting low expression levels of RFC1 micro-RNA in patients with a poor histological response.

Hattinger C.M. et al. (Italian sarcoma group) presented the results of a study whose goal was to determine the prognostic significance of protein expression ERCC1 (excision repair cross-complementation group 1) in biopsy tumor material in patients with localized osteosarcoma who underwent programmed treatment of ISG / OS-oss and ISG / SSG1. A tumor sample was considered positive in the presence of a score of 2-3: score 1 (1-10% of positive nuclei), score 2 (11-50% of positive nuclei), score 3 (more than 50% of positive nuclei). ERCC1-positive tumor (score 2-3) was detected in 30 patients (30%). During the ISG / OS-oss program in groups of patients with ERCC1-negative / score 1 and ERCC1-positive (score 2-3), the 5-year-old RH and BSV tumor variants were 91%, 38% and 57%, 25% (p = 0.001; p = 0.042), with the ISG / SSG1 program - 82%, 64% and 69%, 36% (p = 0.022; p = 0.028), with both therapy programs - 82%, 50% and 62% , 34% (p <0.001; p = 0.006). Consequently, a statistically significant relationship has been established between the ERCC1-positive variant of the tumor and lower rates of 5-year OS and BSV [16].

Nguyen A. et al. (SFOP) presented the results of a study to determine the prognostic significance of TOP2A protein expression (topoisomerase DNA 2 alfa) and the presence of rearrangement of the TOP2A gene in biopsy tumor material in 105 children with osteosarcoma who were treated using the SFOP protocol OS94. Patients with primary metastatic osteosarcoma were 17%. After neoadjuvant chemotherapy, a good histological response was detected in 56 patients (53%), a poor histological response in 49 (47%). Real-time PCR amplification of the TOP2A gene and the TOP2A gene deletion were detected in 21 (21.2%) and 25 (25.3%) patients. In 53 children (53.5%), no rearrangement of the TOP2A gene was detected. A statistically significant relationship was established between the presence of the TOP2A gene rearrangement (amplification and deletion) and the presence of a good histological response after neoadjuvant polychemotherapy (p = 0.004). There was also a tendency to achieve lower rates of 5-year OM and BSV in patients whose tumor cells showed amplification of the TOP2A gene (p = 0.09 and p = 0.06). The expression of the TOR2A protein was determined in 17 patients by immunohistochemistry. Medium (2+) and high (3+) levels of expression were detected in all patients, expression was above 30% in 12 of 17 children (70.5%). There is no statistically significant relationship between the expression of the TOR2A protein above 30% and the presence of amplification or deletion of the TOP2A gene (p> 0.05) due to an insufficient number of observations [27].

Xiao X. et al. Presents the results of a study of a personalized approach to the prescription of chemotherapy depending on the presence or absence of markers of drug resistance in 28 patients with localized osteosarcoma. The average age in the group of patients was 20.1 g. To determine the sensitivity to chemotherapy, the following markers were used: for doxorubicin - expression of TOP2A micro-RNA, mutation of the ABCB1 gene, mutation of the GSTP1 gene; for cisplatin, expression of micro-RNA ERCC1, BRCA1, mutation of the genes XRCC1-exon6 and XRCC1-exon10, for ifosfamide, mutation of CYP2C9 * 3.

At the same time, a high level of sensitivity to ifosfamide was detected in all patients (100%), to cisplatin in 11 out of 28 (39.2%), to doxorubicin in 6 out of 28 (21.4%); medium and high levels of sensitivity to cisplatin in 17 of 28 (60.7%), to doxorubicin in 20 of 28 (71.4%). Chemotherapy, taking into account the

sensitivity of the tumor to drugs, was performed in 8 of 28 patients (28.5%). In this group, only 1 relapse of the disease was detected, while in the rest of the 20 patients 4 relapses of the disease were detected, in 1 case progression during neoadjuvant chemotherapy and in 1 case fatal outcome from toxicity of therapy. The average duration of observation for groups was not indicated and no statistically significant difference was obtained due to the insufficient number of observations [34].

In addition, the study of markers of stem tumor cells CD133 (Prominin 1) and OCT4 (Octamer-binding transcription factor 4), as well as transcription factors STAT3 (signal transducer and activator of transcription 3) and C-MYC (myelocytomatosis viral oncogene homolog), which determines the invasive and metastatic potential of a tumor [32]. Some studies have noted a significant correlation between the expression of CD133 in tumor cells and a higher frequency of metastatic lesions, a lower median of overall survival. A CD133 positive variant was detected in 46 out of 70 (65.7%) patients, in 6 out of 16 (37.5%) in the group with a localized osteosarcoma variant, and in 40 out of 54 (74%) in the group with the primary metastatic osteosarcoma (p = 0.002). The median overall survival rate was statistically significantly lower in the group with a CD133-positive tumor variant (p = 0.000). When conducting the study “Transwell invasion”, a significantly higher invasive potential of the CD133-positive variant of the tumor was established (p <0.05). Real-time PCR established a higher level of expression of OCT4 micro-RNA in a CD133-positive variant of the tumor (p <0.05) [25].

Li J.I. et al. in an experimental model on cell lines showed that about 80% of the cells in the CD133-positive variant of the tumor are in the G0 / G1 phases of the cell cycle (p <0.01). Also, real-time PCR revealed a significantly higher level of expression of the multidrug-resistant gene (MDR1) in the CD133-positive variant of the tumor (p <0.05) [23]. In the works of Tu B. c et al. the significance of activation of the IL6R / STAT3 / p-STAT3tyr705 mesenchymal stem cell signaling pathway to increase the metastatic potential of tumor cells was exemplified by the example of cell lines (Saos 2 and U2-OS). The relationship between the increased expression of p-STAT3tyr705 and the increased expression of the drug resistance markers MRP (multidrug resistance protein) and MDR1 has been established. An increase in sensitivity to doxorubicin, but not to cisplatin, was also noted with inhibition of this signaling pathway [33].

Han G. et al. using cell lines (MG63 and SAOS2) as an example, it was shown that an increase in C-MYC expression leads to activation of the MEK-ERK signaling pathway and an increase in the expression of MMP2 and MMP9, which enhance the invasive and metastatic potential of a tumor [15].

Wu X. et al. investigated the prognostic significance of C-MYC expression in biopsy tumor material in 56 children with osteosarcoma who were treated with methotrexate, cisplatin, adriamycin. Expression of the C-MYC protein was detected in 48 of 56 (85.7%) patients. A statistically significant relationship was established between the presence of C-MYC expression and a decrease in the apoptotic index (p <0.05). In addition, in the group of patients with C-MYC-positive variant of the tumor and the intensity of expression, at 2+ and 3+ a significantly lower 3-year-old OM was established (p <0.05). Consequently, in the works of Tu B., Han G. and Wu X. et al. The significance of transcription factors in the development of drug resistance, invasion and metastasis of the tumor has been established.

Innovative therapeutic approaches are used mainly in patients with metastatic osteosarcoma, relapse and refractory course of the disease. Currently, there are the following key areas: 1) the use of monoclonal antibody preparations; 2) tumor-modifying therapy using nitrogen-containing bisphosphonates; 3) the use of chemotherapeutic drugs affecting various cellular signaling pathways (multi-kinase inhibitors, mTOR inhibitors); 4) the use of drugs that promote the activation of tumor-associated macrophages.

Rossi B. et al. presented the results of a study aimed at determining the expression of VEGF (vascular endothelial growth factor) in a biopsy tumor substrate and in tumor material after neoadvanting chemotherapy (2 courses of MAP) in 16 patients with localized osteosarcoma who received programmed treatment using the SSG XIV protocol. Four levels of expression were evaluated: negative and low - at an expression level <25%, medium - at 25–50% (1+), high - at 50–75% (2+), very high — at> 75% (3+). Medium and high levels of VEGF expression in biopsy tumor material were detected in 11 (6 in medium and 5 in high) out of 16 patients (68.7%). After neoadjuvant chemotherapy and the removal of the primary tumor site, VEGF expression was detected in all samples, and there was an increase in expression in samples that were positive during the initial study.

High and very high levels of expression, increased expression after neoadjuvant chemotherapy were statistically significantly correlated with the localization of the primary tumor lesion in the femur (p = 0.02), with the appearance of local recurrence (p = 0.04) and / or early metastatic lesions in the lungs (p = 0.04), with a fatal outcome from the refractory course of the disease (p = 0.04).

Therefore, the presence of VEGF expression in the biopsy material, an increase in the expression of VEGF after neoadjuvant chemotherapy are factors for poor prognosis of the disease [13]. But this study requires the continuation of the fact that it includes a small number of patients.

Currently, little experience has been gained with the use of the drug buvacizumab in children with osteosarcoma.

Bevacizumab is a partially humanized monoclonal antibody to VEGF - A, IgG1, which realizes its activity through the second type of immunopathological reactions (antibody-mediated complement-dependent cytotoxicity, antibody-mediated cell-dependent cytotoxicity) [15]. Back in 1999, employees of the Memoroal Sloan-Kettering Cancer Center presented the results of a study assessing the effect of ErbB2 expression (erb-b2 receptor tyrosine kinase 2) on the nature of the histological response after neoadjuvant polychemotherapy and on the rates of OS and BSV. The study included 53 patients. ErbB2 overexpression was detected in 42% of patients in the entire study group, in 50% with metastatic variant and in 76% at the time of detection of relapse or refractory course of the disease, and also statistically significantly correlated with a poor histological response (p = 0.02) and BSV (p = 0.05). The 5-year BSV in patients with a localized version of osteosarcoma and ErbB2-positive status was 47%, with ErbB2-negative status - 79% [13].

Conflicting data on the prognostic significance of ErbB2-positive status in patients with localized osteosarcoma were obtained.

In 2002, the Japanese Osteosarcoma Group (Japanese Osteosarcoma Group) published the results of a study that included 155 patients with localized osteosarcoma from 1984 to 1995. At the same time, the 5-year BSV in patients with ErbB2-positive status was 45%, with ErbB2-negative status - 72%.

In 2014, the American Pediatric Oncology Group (COG) presented

completely different results of the study, which from 1999 to 2002 included 135 patients with localized osteosarcoma. Only 13% of patients showed ErbB2-positive status. The 5-year RR in patients with ErbB2-positive status was 73%, with the ErbB2-negative status - 72%, the 5-year RR - 59% and 69%, respectively. No statistically significant difference in survival was observed [14]. Thus, it was confirmed that ErbB2 can be considered as a potential target for targeted therapy for metastatic variant, relapse and refractory course of the disease.

Trastuzumab is a partially humanized IgG1κ monoclonal antibody to ErbB2, which also realizes its activity through a second type of immunopathological reaction (antibody-mediated complement-dependent cytotoxicity, antibody-mediated cell-dependent cytotoxicity). The drug was administered at a dose of 4 mg / kg in the first week, then 2 mg / kg 1 time per week (34 in total) only in patients in whose tumor substrate ErbB2 expression was detected. In the group with trastuzumab, a good histological response was detected in 56% of patients, without trastuzumab - 40%, a poor histological response - 44% and 60%, respectively. At the same time, the 3-year OS and BSV in the group of patients who received treatment with trastuzumab accounted for 59% and 32%, and in the group of patients who received treatment without trastuzumab - 50% and 32%. Consequently, the use of trastuzumab with polychemotherapy MAPIE led to an increase in the frequency of achieving a good histological response, but not to an increase in the rates of OS and BSV [7]. Of particular interest is tumor-modifying therapy using nitrogen-containing bisphosphonates. Currently, the following mechanisms of action of nitrogen-containing bisphosphonates have been identified, which are represented by the activation of tumor cell apoptosis by the caspase mechanism (indirectly through Rb and P53 protein) and without the participation of the caspase mechanism (an increase in AIF — apoptosis of the inducing factor); increased expression of TRAIL-DR5 (TNF-related apoptosis-inducing ligand - death receptor 5, TRAIL - induced apoptosis); a decrease in RANKL expression (Receptor activator of nuclear factor kappa-B ligand - ligand of nuclear factor activation receptor kB) in osteosarcoma cells, which leads to suppression of tumor cell proliferation, osteoclast activity, changes in tumor microenvironment, bone resorption and risk of metastasis; activation of γδT cellular cytotoxicity; activation of the tumor-associated macrophages [23].

At present, a rather small experience has been gained of using these drugs in children with osteosarcoma.

Meyers P.A. et al. published the results of a study on the combined use of pamidronate with MAP chemotherapy. The study included 40 patients, 32 in the age group up to 18 years, 29 with a localized osteosarcoma variant, 11 with a primary metastatic osteosarcoma variant. In accordance with the program, pamidronate was administered once a month at a dose of 2 mg / kg 48 to 72 hours after adriamycin, methotrexate, a total of 12 administrations. Surgical removal of the primary tumor lesion was performed at week 11. Adjuvant chemotherapy started at week 13. Removal of metastatic foci was carried out individually at the stage of adjuvant therapy.

The frequency of achieving a good and poor histological response is not indicated. However, fairly high rates of 5-year OS and BSV were obtained: 93% and 72% in patients with localized osteosarcoma, 64% and 45% in patients with metastatic osteosarcoma [25]. The American Pediatric Oncology Group (COG) presented the results of the pilot protocol AOST06P1 aimed at studying the combined use of zoledronic acid with the polychemotherapy of MAPIE in children with the primary metastatic osteosarcoma. This study included 24 patients. Zoledronic acid was administered at a dose of 1.2 - 3.5 mg / m2 in each course of chemotherapy. Piperno-Neumann S. et al. presented the results of a phase 3 randomized study OS 2006, the purpose of which was to identify the potentiating effect of zoledronic acid when used together with polychemotherapy MIE and MAP.

The study included 217 children, 107 in the control group and 110 in the group with zoledronic acid. Groups of patients were statistically significantly comparable by sex, age, foci of primary and metastatic lesions, and histological variant of the tumor.

Zoledronic acid was administered at a dose of 0.05 mg / kg (maximum dose of 4 mg) with each course of chemotherapy (IE and AP). Neoadjuvant chemotherapy consisted of 2 courses of IE (ifosfamide (I) 12 g / m2, etoposide 300 mg / m2) and 7 administrations of high-dose methotrexate ((M) 12 g / m2). Surgical removal of the primary tumor lesion was performed at week 14. Adjuvant chemotherapy included 2 courses of MIE in the group with a good histological response and 5 courses of MAP in the group with a poor histological response. A good histological response after neoadjuvant polychemotherapy was achieved in 73% of patients. However, there was no statistically significant difference in achieving a good histological response, in terms of OS and BSV in groups of patients who received programmed treatment with or without zoledronic acid. The number of events in the group with zoledronic acid was 42% (47/110), in the group without zoledronic acid - 31% (34/107). Consequently, this study shows the high effectiveness of chemotherapy courses for IE in combination with methotrexate in the neoadjuvant regimen. The presence of the potentiating effect of zoledronic acid has not been proven.

In the treatment of refractory forms of osteosarcoma, drugs are also used that affect various cellular signaling pathways. Understanding the mechanisms of tumor activation opens up the possibility of using multikinase and mTOR (mammalian target of rapamycin complex) inhibitors.

Takagi S. and Peng N. et al. In an in vitro experiment on cell lines (SaOS2, MG63, HOS), pathogenetic mechanisms of cytokine-induced tumor transformation and proliferation were shown through the activation of VEGF / VEGFR / PI3K (Phosphatidylinositol-4,5-bisphosphate 3-kinase) / AKT (Protein kinase B) and the PDGFR (Platelet-derived growth factor receptor) / PI3K / AKT signaling pathways. The most studied drugs from this group are currently sorafenib (nexavar) and everolimus. Sorafenib is a non-selective multi-kinase inhibitor that inhibits the activity of various cellular signaling pathways, in particular VEGFR1, VEGFR2, PDGFRα, PDGFRβ, while everolimus is an mTOR inhibitor. Ymera P. et al. of the Italian Sarcoma Group published the results of a preclinical study (in vitro and in vivo), which noted the mutually potentiating antitumor effect of everolimus and sorafenib on osteosarcoma cell lines (KHOS, MNNG-HOS, U2OS). The effect of everolimus and sorafenib on mTORC1 / mTORC2 is manifested in a decrease in the expression of mTORC1 and an increase in the expression of mTORC2, which provides proapoptotic and antiproliferative effects. With the combined use of everolimus and sorafenib, the expression of both mTORC1 and mTORC2 decreases.

From 2008 to 2009, Grignani G. et al. of the Italian Sarcoma Group conducted a second phase of clinical trials of the drug sorafenib in patients with relapse and refractory osteosarcoma. The study included 35 patients with osteosarcoma

in the age group over 14 years. Partial response was achieved in 5 (14%) patients, disease stabilization in 12 (34%) patients. The overall response rate was 48%. At the same time, 4-month progression-free survival was 45% (15 out of 35).

Thus, taking into account the data of 2008 studies (use of sorafenib in mono mode) and 2011 (using a combination of sorafenib with everolimus), it can be said that the combination of sorafenib with everolimus leads to an increase in the overall response rate, an increase in survival rate without disease progression within 6 months However, by the year this difference disappears.

Compared to international data (Italian sarcoma group) in the presented study, the achievement of a partial response, stabilization of the disease and the overall response rate were significantly higher.

Currently, a number of studies aimed at studying the role of tumor-associated macrophages. Activation of tumor-associated macrophages can be carried out through the use of preparations of liposomal tripeptides (mifamurtid), preparations of interferons (interferon alpha-2A).

Meyers P.A. et al. presented the results of the randomized study CCG 7921 / POG 9351, which was conducted from 1993 to 1997. The study included 662 patients with a localized version of osteosarcoma.

A feature of line A therapy was the use of 2 courses of neoadjuvant chemotherapy for MAP; in the line of therapy B: 2 courses of neoadjuvant chemotherapy MAI, alternating courses of MAR and MAi at the stage of adjuvant chemotherapy. Surgical removal of the primary tumor lesion was performed at week 10. Mifamurtid (MTR) was administered at a dose of 2 mg / m2 2 times a week for 12 weeks, then once a week for 24 weeks according to randomization. The mechanism of action of mifamurtid (MTP) is to activate monocytes / macrophages with antitumor activity, which is realized as a result of binding to specific receptors TLR4 (toll-like receptor 4) and NOD2 (nucleotide-binding oligomerization domain 2 receptor) with a subsequent change in the activity of cellular signal pathways (ERK1 / 2 - extracellular-signal regulated kinase 1/2), NF-kB - nuclear factor kappa-B, AP1 - adapter protein 1). After removal of the primary tumor focus, a good histological response in group A was achieved in 42% of patients, in group B in 48%, a poor histological response in group A - 58%, in group B - 52%. At the same time, the 6-year-old RR was 74%, without the use of MTP - 70%, with the MTR - 78%; BSV - 64%, without the use of MTR - 61%, with MTP - 67%. In group A: OS without the use of MTR - 71%, with MTR - 75%; BSV without MTR -64%, with MTR - 63%. In group B: OS without the use of MTR - 71%, with MTR - 75%; BSV without MTR -64%, with MTR - 63%. The addition of MTP to polychemotherapy led to a statistically significant increase in the 6-year OS from 70 to 78% (p = 0.03), and there was a tendency to an increase in BSV, mainly in group B (p = 0.08) [26].

Kubo T. et al. published the results of a pilot study that determined the prognostic significance of the expression level of interferon α / β receptors in 40 patients with localized osteosarcoma who received treatment according to the NECO95J program. The expression of interferon α / β receptors was detected in 45% of patients. When conducting multivariate statistical analysis, a significant association was observed between the expression of interferon α / β receptors and 5-year-old OM and the survival free of metastatic lesions (VSMP). The 5-year OM, in the presence of expression of the α / β interferon receptor in the tumor substrate, was 81%, with no expression, 47% (p = 0.043), the 5-year HSMP - 75% and 41% (p = 0.023). This study confirms the possibility of using interferon preparations in the treatment of osteosarcoma in patients with overexpression of α / β interferon receptors [12]. Bielack S.S. et al. presented the results of the EURAMOS1 study in patients with a good histological response after neoadjuvant MAP chemotherapy. In the age group up to 30 years, the MAP line of therapy was carried out to 359 patients, the MAP INF line - 2b - to 357 patients, in the age group up to 20 years - 333 (92.7%) and 332 (92.9%) patients. Groups of patients are statistically significantly comparable by gender, age, localization of the primary tumor lesion, the presence of a metastatic lesion, the histological variant of the tumor. In accordance with the program, pegylated INF - α - 2b was administered at a dose of 0.5 mg / kg (at a maximum dose of 50 mg) once a week for 4 weeks, then 1 mg / kg (at a maximum dose of 100 mg) 1 time per week (from 30 to 104 weeks of programmed treatment). In a group of 630 patients with a localized version of osteosarcoma, 135 events were detected, 72 in patients who received the MAP therapy line, 63 in patients who received the MAP INF therapy line - 2b. At the same time, the 3-year BSV was 77% and 80%, respectively. Therefore, the use of INF - α - 2b as a supportive therapy after MAP in patients with a good histological response did not lead to an increase in BSV [6].

Conclusion. Thus, the results of treatment of children with primary metastatic osteosarcoma, relapse and refractory course of the disease remain unsatisfactory. Molecular biological factors that determine sensitivity to chemotherapy, invasive and metastatic potential of the tumor, as well as the prognosis of the disease, among which special attention is deserved: expression of MGMT protein, methylation of the promoter part of the MGMT gene, expression of ERCC1 proteins, VEGF, CD133, p -STAT3tyr705, C-MYC, expression of RFC1 micro-RNA and the presence of rearrangement of the TOR2A gene. It is important to note the following fact that there was no comprehensive assessment of the value of these markers for the histological response to neoadjuvant chemotherapy and survival rates in patients with osteosarcoma.

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POINT OF VIEW

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YAKUTIA'S LONGEVITY PHENOMENON – MYTH OR REALITY

ABSTRACT

In the Soviet years the idea was formed, that Yakutia was one of the centers of longevity in the country. Based on the study of archival materials and census data, it was established that this statement was erroneous. The reasons for spreading this false statement are shown. As an illustrative example, the church and statistical documents of the Oymyakonsky and Suntarsky uluses were considered as areas of Yakutia, where the so-called longevity phenomenon was most pronounced. The age of specific residents of Oymyakonsky district from the family list for 1928 was compared with the lists compiled from 1942 to 1946, as a result of which it was established that in most cases the villagers provided overestimated information about their age.

Keywords: demography, Yakuts, aging, longevity, Yakutia.

In 1897, the first general population census was conducted in Yakutia, the results of which found that 1043 centenarians live in the region, including 90 people aged 100 years or more [9]. In connection with the above, at the end of 1898, the manager of the Central Statistical Committee addressed a letter to the governor of the Yakutsk Oblast V.N. Skripitsyn, asking to provide detailed information about each resident of Yakutia who had crossed the centenary: *"... A special survey is required about each one, in the ways of understanding all their living conditions and the accuracy of the age shown ..."* [16]. Attached to the letter were 50 copies of questionnaires with 38 questions regarding the respondent's lifestyle, physical condition, and heredity.

On February 15th, 1899, by order of the governor, 10 questionnaires were sent to the Yakutsk Oblast District Police Officer, Olekminsky – 12, Vilyuisky – 4, Verkhoyansk – 5 [18]. Later it turned out that when filling them, the age of 19 surviving respondents living in the districts by that time was recorded from hearsay, in connection with which Skripitsyn demanded additional confirmation: *«…I consider it a good practice – in all 19 cases – to ask local clerks to verify the validity of testimony at the age using metric records and, if it is impossible to extract data from the birth records, then trace the testimony of age at confessions and marriage records. In the absence, for any reason, of a second copy of these books at the priests, detailed information will be needed about the time for the provision of metric books to the spiritual consistory with the exact designation of the name of the parish…»* [17].

Although the search continued for more than 2 years, in most cases it was impossible to establish the exact date of birth. This was mainly due to the lack of information about these people in church documents, since many parishes appeared later than the date of birth of the respondent. But in the case when it was possible to establish the necessary information, it turned out that the respondent was much younger than expected. So, at that time, the oldest of the verified centarian of Yakutia was 94-year-old Anna Ivanova Maksimova from the Vilyui District [19], while the rest of the "aged" were 70-80 years old. In this regard, a rather indicative was the letter of the Zemstvo Assessor of the 3rd District of the Yakutsk Oblast dated December 10th, 1901 addressed to the District Police Officer of the Yakutsk Oblast*: «…I received the honor of submitting information about the three elderly persons of Dyupsinsky Ulus and informing you that according to the attached certificates of confessional books, these persons in the year of the general census were not 100 years old, but much less – they were Matrena Ivanova Dmitrieva (according to the confessional book: Matveyeva), only 72 years of age; Anisye Ivanova Ushnitskaya (according to the confessional book: Matrena Ushnitskaya) is only 73 years old, and Kapiton Porokhov is only 76 years old. These certificates from confession books are given by clerks and deserve more confidence than the testimony given during the census, since the Yakut who can remember their years well are is more likely an exception, in most cases Yakuts tend to lose count of their years and continue the counting according to presumptive and major figures, for example: "Min (*Yakut for

"I am" – translator's note*) a hundred years old, mind you." and so on. In view of this, questioning these people on question sheets is losing all its scientific significance ..."* [20].

Confirmation of a small number of centarians in Yakutia in the XIX century also came from the data obtained from the family census for 1858 [27]. For example, out of 1,121 people living in Oymyakono-Borogonsky Nasleg (now Oymyakonsky Ulus), only 16 (1.4%) were older than 70 years, while the most elderly were 85 years old. The average age of the population was 27.8 years, the average age of the deceased was 49.2 years. Similar information was obtained when analyzing information from the metric books [25, 26]. So, from 1907 to 1910, the average age of the dead Oymyakon residents from 4 years and older was 49.1 years (n = 96). At the same time, the share of people from 70 years and older was 25%, from 90 years and over 5.3%. The oldest of the deceased was 96 years old at the time of death.

The indicators under consideration in the Suntarsky District differed, but insignificantly, according to the data of the register of the Krestiakh Church of the Three Saints for 1880, 1885, 1892, 1899-1909, 1911, and 1912. The average age of the dead aged 4 years and older was 47.8 years (n = 709 people), the proportion of people aged 70 years and older was 16.9%, and for those aged 90 years and older it was 1.7%. In this case, the maximum age was 100 years (1 person).

Thus, it is obvious that there were no outstanding indicators on life expectancy from the end of the XIX to the beginning of the XX centuries in these 2 uluses, even though they were later viewed as one of the foremost in the Republic for their population's longevity.

After the end of the Russian Civil War, work on statistical registration of the population in Yakutia resumed. Unfortunately, as in the previous census, age data was collected by survey. As a result, it turned out that in 1926 in the Republic the number of Sakha centenarians was 1,248 people, including 176 people. at the age of 100 years or more [3]. That is, in terms of 100 thousand Yakut population, the number of people aged 90 years and older was 529 people (Table 1). But considering that in those years the overwhelming majority could neither read nor write, this fact being taken on trust is unacceptable. For example, among the Sakha from 70 years and older, only 0.11% were literate and this figure remained equally small until the 1940s. Working at the Oymyakon airport from 1943 to 1946, the radio telegraphist E.F. Vyatkina, in her memoirs, wrote the following *"…We always treated Yakuts with great respect, but their lives were awful – illiteracy, complete insecurity, subsistence farming and its primitive economy... …Once we asked a his age. He went: "Thirty." We asked him how he had counted it. That's when he quickly began counting on his fingers: spring, summer, spring, summer, etc. We then realized that he was 15 years old..."* [13].

Dynamics of the number of Sakha centenarians in the period from 1928 to 2010 (according to statistical compilations)

Indicator	Years				
	1928	1950*	1970	1989	2010
Number of people 90 years and older	1248	1023	880	н/д	316
100 years and older	176	162	100	76	13
Number of long-livers per 100 thousand / population	529	454	308	н/д	68

Taking into account the fact that the data of the first Soviet census are doubtful, we verified 11 people under the age of 50 years and found that the number of years they lived corresponded to birth dates recorded in metric books. As for the older generation, the answer here is ambiguous. When comparing the ages of mothers and their children, it turned out that at least 5 women in the nasleg theoretically were 55-67 years old when giving birth. Unfortunately, it is not possible to clarify the age of these women due to the lack of necessary documents.

Nevertheless, we compared the age of specific individuals (91 people) from the family list of the district for 1928 [24] with their age, which is listed in the lists of exemptions from tax for 1942 and 1944. [21, 22], in the lists of labor soldiers mobilized by the Oymyakonsky Regional Military Commissariat for 1945-1946. [13] and in the lists of personnel hunters for 1946 [23].

We found that age is true or almost true (± 1 year) only in 13.2% (12 cases), understated in 5.5% (5 cases, on average by 3.6 ± 0.8 years), and 81.3% (74 cases) were significantly overstated. For example, there were cases when people indicated an age of 131 and 140 years, whereas in fact they were 81 and 83 years old, respectively. Even without these 2 incredible cases, the average increase in age was 8.9 ± 0.7 years, while 6 people overestimated their age by 20 years or more.

Perhaps a decisive role in the overestimation of age during the war years could have been played by the decree of the Presidium of the Supreme Soviet of the USSR of July 3rd, 1941, establishing a temporary allowance for agricultural tax and personal income tax during wartime. According to it, the farms of collective farmers and individual farmers who are unable to work due to old age (men: 60 and older, women: 55 and older) who have no able-bodied family members were exempted from paying the tax. According to our data, by 1942, 25.3% (23 people) of all those who overstated their age could enter the category of benefit recipients.

Another good reason for deliberately raising the age in the northern regions could be an attempt to avoid mobilization to the front. During 1944-1945, Verkhoyansky, Oimyakonsky and Srednekolymsky districts were planning to mobilize 600 people for the construction of the Krasnoyarsk-Uelkal airfield airports [28]. However, given that the collective farms also needed to fulfill their plan, but there was a catastrophic shortage of people, it is possible that the heads of the agricultural artels introduced these distortions intentionally.

Most likely, the distortions of the age data continued into the post-war period. For example, the real age of a resident of the First Borogonsky Nasleg F.A. Ammosov in 1944 was 81, although he indicated that he was 76 years old. However, in 1957, he was described as a 109-year-old [11], and in 1966, as a 117-year-old resident [15], whereas in fact he was 94 and 103 years old, respectively. By the way, Ammosov died at 105 and should be considered the record holder of the Oymyakonsky District in longevity.

Apparently, the situation described above with the overestimation of age was observed throughout the rural areas of the Republic, as a result of which, after the war, mass media began to regularly report on the so-called Yakut phenomenon of longevity [4-8, 11, 12, 15]. As a rule, such articles always had political overtones – the authors of the articles actively conveyed to the reader the idea that the old men described by them are living witnesses of the improvement of living conditions in the country after the establishment of Soviet power.

Beginning in 1970s, as a result of the natural change of generations, the number of "long-livers" from the 1950s and 1960s began to shrink. Some researchers, taking the statistics of those years on trust, attributed this to environmental

degradation, changes in lifestyle, type and quality of nutrition of the population [2, 10]. But the development of medicine and a significant improvement in the living conditions of the population over the past decades should have sufficiently leveled all the mentioned negative aspects. In our opinion, the main reason for reducing the number of centenarians in the Republic is not environmental factors, but the normalization of statistical records of the population.

Notwithstanding the foregoing, we found real cases of supercentarians (110 years or more) among the local population of Yakutia. For example, the 117-year-old Varvara Konstantinovna Semennikova (Dyakonova) who lived in the Saskylakh Village of the Anabarsky Ulus and whose age was verified by the staff of the National Archive of the Sakha (Yakutia) Republic. As of November 2017, Semennikova was recognized as the oldest inhabitant of the planet [14].

Nevertheless, the widely publicized assertion that Yakutia was once the center of longevity in the USSR is highly doubtful, and this issue requires additional and more in-depth study not only from health workers, but also from historians.

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CLINICAL CASE

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THE CHEMATOLOGICAL DISORDERS IN ADOLESCENT ON THE BACKGROUND OF TUBERCULOSIS TREATMENT

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ABSTRACT

This article describes a clinical case of hematotoxic adverse reaction in a patient on the background of anti-tuberculosis chemotherapy. It has been established that the appearance of anemia of mixed genesis with thrombocytopenia in a patient is associated with the intake of PASK.

PASK instruction indicates the appearance of thrombocytopenia, leukopenia in rare cases. On the background of the replacement therapy with blood components and the cancellation of anti-TB drugs, blood counts returned to normal.

The probable degree of reliability of cause-effect relationship by adverse side reaction is established.

Currently, the patient's condition is satisfactory. The patient feels good. The function of hematopoiesis is restored.

Keywords: chemotherapy, thrombocytopenia, anti-tuberculosis therapy, adverse reaction, anemia, leukopenia.

A change in the parameters of the General blood test is a frequent phenomenon in patients with tuberculosis. They reflect the severity of intoxication, especially the reactivity of the body, the degree of tissue damage, the presence of concomitant pathology and violations of nutritional status, in rare cases; indicate a specific lesion of the hematopoietic system [1]. As a rule, successful tuberculosis treatment is accompanied by a normalization of the haemogram. However, in some patients during anti-tuberculosis therapy, there are negative shifts in hematological indicators, indicating an undesirable side effect of anti-tuberculosis drugs. The frequency of hematological adverse reactions is low-from 1.2 to 22.8% [3, 4]. Disorders in the blood system are a rare but potentially dangerous complication of anti – tuberculosis chemotherapy. Anti-tuberculosis drugs can cause a decrease in certain pools of blood cells due to suppression of their formation in the bone marrow or accelerated destruction in the bloodstream [2]. We present a clinical case of adverse reaction with tuberculosis chemotherapy

The aim: to show the clinical observation of reactions due to tuberculosis therapy in a patient of 20 years.

The results of observation:

From the history of the disease: Patient D, female, born in 1998, hospitalized in the children's Department №2 Research and Practice Center for Tuberculosis of Republic Sakha (Yakutia) on 05.07.2016.

From the anamnesis it was found out that it consists on the dispensary account since May 2016 on contact with mother. Mother is patient with infiltrative tuberculosis of the lower share of the right lung, Mycobacterium tuberculosis (MBT) + (sensitivity of Mycobacterium tuberculosis to anti-tuberculosis drugs is kept). Clinically, there is a constant sub febrile temperature; the state of health does not suffer much. On radiographs of the chest organs detected focal shadows in S1, S2, S3, S4, S6 of the right lung and S1-2, S3, S6 of the left lung in the phase of infiltration and disintegration cavities, the increase of intrathoracic lymph nodes. On 14.07.2016 by medical commission No. 292 exhibited clinical diagnosis: A15.0 Disseminated pulmonary tuberculosis in the phase of infiltration and decay Mycobacterium tuberculosis (+).

From the protocol of medical commission for childhood: assigned 1 chemotherapy regimen intensive phase (h 0,6 +R 0,45+Z 1,5+e 1,2) 18.10.2016 repeated medical commission to assess the effectiveness and outcome of tuberculosis chemotherapy №246 for routine monitoring. The medical commission agreed to: recommend the chemotherapy should be extended to 120 doses. On 15.11.2016, medical commission was carried out to assess the effectiveness and outcome of tuberculosis chemotherapy No. 267 under planned control. The patient received 120 doses of chemotherapy regimen I. In dynamics marks the cessation of bacterial excretion, remain small decay cavities S1-2 of right lung. Taking into account the data, it is recommended to extend the intensive phase of chemotherapy to 150 doses. On 09.12.2016 was consultation thoracic surgeon.

Conclusion after the consultation: surgical treatment is indicated. On 20.01.2017 patient transferred to the surgical department. On 25.01.2017 doctors were held 1 stage of surgical treatment: resection S1-2 left lung. On 09.02.2017 was held the 2nd stage of surgical treatment: atypical resection S1-3 in the right lung. From 27.02.2017, the postoperative period was uneventful. Patient was transferred to the children's Department №2 with the diagnosis: Disseminated pulmonary tuberculosis with the formation of tuberculosis. Resection S1-2 left lung from 25.01.2017, S1-3 right lung 09.02.2017.

01.03.2017 was medical commission to conduct analysis of the effectiveness and outcome of therapy No. 46 for corrective control. Medical commission solution recommended therapy with 02.03.17: isoniazid, pyrazinamide, etambutol, PASK for 2 months. For 4 months to appoint a continuation phase. The next control was in May 2017, after receiving 60 doses.

In this time patient periodically notes the appearance of pain in the joints of the upper and lower extremities, the appearance of stiffness in the joints. Visually, the joints are not changed. No swelling or hyperemia.

On 12.03.2017 complaints of runny nose, cough, sore throat, joint pain. The diagnosis: a respiratory catarrh.

On 13.03.2017, the patient complained of pain in the joints of the upper and lower extremities, General weakness, and an increase in body temperature to 37.

On 14.03.2017 patient was examined by a pediatrician. State of health does not suffer; the general condition is closer to moderate severity. The body temperature was 36.6. Heart rate 90 bpm.

Conclusion: Normochromic anemia 3 degree. Thrombocytopenia.

Recommended: to appoint the analysis of blood and urine. As a result

of the survey the following results were obtained: blood counts was obtained 14.03.2017: erythrocytes of 2.06, 62 hemoglobin, leukocytes 4.7, 17 thrombocytes, erythrocyte sedimentation reaction 57 mm/HR, segmented granulocytes 55, eosinophil 3, monocytes 4. According to the results of blood analysis revealed anisocytosis, severe normochromic anemia. (table 1)

Biochemical analysis of blood from 15.03.17: Total protein – 70 g/l, albumin 37 g/l, urea – 8.0 mg/DL, creatinine was 77 μmol/l, total bilirubin 22 mmol/l, direct bilirubin – 10.2 mmol/l, ALT– 33 U/l, aspartate aminotransferase (AST) is 25 U/l, glucose 4.6 mmol/l, kalium 4.8 mmol/L.

On 14.03.2017 examination of the doctor, head of the Department of phthisiology. The patient complains of coughing with sputum, according to the patient brown-yellow. During the inspection of the tonsils the tongue is geography. Heart rate 90 beats 1 min. Conclusion: thrombocytopenia. Severe anemia.

15.03.20. Cough persists. Doctors obtained 30 ml of sputum, mucous nature without pathological impurities. The review radiography of the chest organs, ultrasound of abdominal organs is recommended.

It is noted in blood tests from 13.03.17 (Table 1) the appearance of a picture of severe normochromic anemia, possibly associated with the administration of chemotherapy. In order to exclude internal bleeding, urgently appoint a review x-ray of the lungs in 2 projections, ultrasound of the abdominal cavity. On the radiograph in 2 projections: state after 2-sided resection. Behind the first and second rib of the right and in the first intercostal space of the left lung, thin chains of tantalum seams, adjacent lung tissue, areas of fibrous consolidation are determined. Compaction of the Para costal pleura in 4-5 intercostal left lung to 4 mm.

Conclusion: Disseminated tuberculosis. Areas of fibrous consolidation are determined. Compaction of the Para costal pleura in 4-5 inter costal left lung to 4 mm.

On 15.03.2017 Consultation with the chief freelance hematologist Ministry of Health: to connect the treatment of vitamins, replacement therapy. According to the chief freelance hematologist of Ministry of Health the appearance of anemia is associated with chemotherapy.

On 15.03.2017 was examination of anesthesiologist-resuscitator. At the time of examination, the patient is conscious. Clinical manifestations of internal bleeding were not revealed. There are no respiratory or hemodynamic disorders. According to laboratory data, there is critical thrombocytopenia and severe anemia. To carry out transfusion therapy with blood components, the patient under the control of a transfusiologist is transferred to the Department of anesthesiology, intensive care and intensive care (OARIT). The General condition was regarded as serious. The contact is available. Tongue wet, clean skin clean pale dry. Turgor and elasticity are preserved. Breath adequate is conducted in all departments. Heart sounds are loud, rhythm is sinus, no noise. Pulse 80 beats per 1 min. CD 18. The abdomen is soft, painless, peristalsis auditioned. The liver is not increased. The diagnosis: Thrombocytopenia of unknown etiology.

Recommendations: to determine the blood group, rhesus factor with genotypes.

On 16.03.2017 the doctors held a consultation. The medical commission diagnosed Disseminate pulmonary tuberculosis. MBT (+) 1A DU, A15.0. Resection of the S 1-2 of the left lung, S1-3 right lung. Severe normochromic anemia (Table 1). Recommended: anti-tuberculosis drugs to cancel before the normalization of blood parameters, prescribe replacement therapy with blood components, vitamins B6, B12, ascorbic acid, dynamic monitoring of blood parameters. On 16.03.2017 the medical card of the patient was checked by the pharmacological control service, as a result, an act was drawn up, indicating the need to establish a causal relationship of the appearance of anemia of mixed genesis with thrombocytopenia associated with taking anti-tuberculosis drugs. In the instructions of the drug PASC indicated adverse reactions in the form of thrombocytopenia in rare cases.

19.03.2017 12.00 According to laboratory data, there is a significant positive trend in the form of normalization of blood parameters (Table 1).

29.03.2017. Medical commission №64 was conducted. Solution: the occurrence of mixed-type anemia with thrombocytopenia is associated with PASK, which was appointed on March 3, 2017 due to the need to resume intensive chemotherapy phase 4 with anti-tuberculosis drugs after surgical treatment in accordance with Federal clinical guidelines (2014) in conjunction with H, E, Z.

In the PASK instructions, thrombocytopenia and leukopenia are rarely allowed. On the background of replacement therapy with blood components and cancellation of anti-TB drugs, blood counts returned to normal on the 8th day of treatment.

In connection with the above, a probable degree of reliability of a causal relationship by an adverse side reaction has been established.

On March 29, 2017, a notice was sent to the Office of Department of Russia health control Republic Sakha (Yakutia) on adverse effects, undesirable reactions.

Currently, the patient's condition is satisfactory. The patient feels good. The hematological complication was arrested; the blood formation function was restored.

Findings:

1. Changes in blood test indicators from 13.03.2017, the appearance of anisocytosis in the blood test, severe

General blood count

Date	06.07.16	05.08.16	13.03.17	16.03.17	19.03.17	23.03.17	30.03.17
WBC	7,5 10^9/l	6,7	4,7	2,0	6,4	6,3	5,8
LYM#	2,5 10^9/l	1,7	1,6	0,6	2,7	2,0	1,5
MID #	0,5 10^9/l	0,6	0,2	0,2	0,9	0,4	0,5
GRA#	4,5 10^9/l	4,4	2,9	1,2	2,8	3,9	3,8
LYM %	32,9	25,8	33,7	31,1	42,8	32,2	26,0
MID%	6,5	8,3	5,3	8,1	14,2	6,8	8,4
GRA %	60,6	65,9	61,0	60,8	43,0	61,0	65,6
RBC	4,30 10^12/l	4,03	2,06	1,91	3,12	3,13	3,45
HGB	100 g/l	93	62	53	89	95	108
MCHC	297 g/l	300	336	325	330	338	326
MCH	23,2 pg	23,0	30,0	27,7	28,5	30,3	31,3
MCV	78,3 fl	77,0	89,4	85,8	86,5	90,0	96,0
RDW– CV	18,0 %	19,2	16,3	17,5	16,7	15,6	17,7
RDW-SD	46,9 fl	50,6	52,4	51,6	51,6	47,9	58,8
HCT	33,6 %	31,0	18,4	16,3	26,9	28,1	33,1
PLT	324 10^9/l	269	17	17	53	208	611
MPV	7,4 fl	6,8	9,5	8,6	8,8	8,3	6,9
PDW	15, 3	15,4	17,6	17,9	16,5	15,9	15,3
PCT	0,239%	0,182	0,016	0,014	0,046	0,172	0,421

normochromic anemia appeared after taking PASK in combination with other anti-tuberculosis drugs, which were prescribed in accordance with Federal clinical guidelines (2014) for the diagnosis and treatment of tuberculosis in children and adolescents. The changes are probably associated with inhibition of bone marrow hematopoiesis while taking the PASK drug.

2. According to the order of the Ministry of Health of the Russian Federation of 26.08.2010 No. 757n "On approval of the procedure for monitoring the safety of drugs for medical use, registration of side effects, serious adverse reactions when using drugs for medical use" after excluding other factors, a probable degree of reliability of causation was identified an adverse effect of adverse reactions to PASC.

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A CASE OF RARE LOCALIZATION OF EXTRAPULMONARY TUBERCULOSIS AND SCREENING WITH CROHN'S DISEASE

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ABSTRACT

The article speaks about the clinical case of rare localization of extrapulmonary tuberculosis, abdominal tuberculosis in incurable stage. **Introduction.** Abdominal tuberculosis is characterized by polymorphism of clinical presentation, and sometimes proceeds only with a fever without any symptoms, characteristic for diseases of gastrointestinal tract. Intestinal process localization can arise at any stage of primary and secondary tuberculosis development. Sometimes it develops as a separate disease in the form of the circumscribed lesion of ileocecal or other part of the intestine. [1]. Diagnostics of extrapulmonary tuberculosis localizations is difficult, this disease tends to proceed hidden, behind a mask of other pathological processes [2,3,4]. Unfortunately, there are no many researches on extrapulmonary forms of tuberculosis that cause late detection, more frequent at uncurable stage [4]. **Research objective:** Description of a clinical case of rare localization of tuberculosis and differential diagnostics with Crohn's disease. **Materials and research methods:** we present some data of clinical supervision of the patient with abdominal tuberculosis: infiltration-ulcer tuberculosis of intestine with involvement of iliac and colon (MTB (+), analysis PCR-RV). Tubercular mesadenitis. Extensive miliary dissemination of serous membranes of abdomen, focal generalization in the liver, spleen, in the upper lobe of the right lung (AFB (2 +), luminescent method. Complications of the basic disease: Punching of tubercular ulcers of iliac, cecum and sigmoid guts. Diffused purulent - stool peritonitis. **Results and discussion:** Patient A. was admitted to «Republic Hospital №2–Emergency Center» in February 19, 2018, at 12.13 p.m. Diagnosis on admission: Crohn's disease with a lesion of cecum, ascending colon, active stage. Severe degree. Peritonitis. After preoperative preparation the patient was operated according to the emergency indications. Operation course. Date 19.02.2018. Time: the beginning – 14.55, the end - 16.40. Operation: Subtotal colectomy. Remote macromedication: large gut with 40 cm of iliac. Postoperative diagnosis: Crohn's disease with a lesion of large and small intestines. Active stage, severe degree. Perforation of ileac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent - fecal peritonitis. A terminal stage. 19.02.2018 at 20.00. Cardiac arrest happened on the background of the intensive therapy AP 0/0, heart rate 0. Resuscitation actions without effect were within 30 min. Biological death was verified at 20:30. **Postmortem diagnosis.** Basic: Crohn's disease with a lesion of small and large intestines. Active stage, severe degree. Perforation of iliac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent-stool peritonitis. A terminal stage. Complications of the basic diagnosis: Perforation of iliac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent-stool peritonitis. A terminal stage. Cachexia. A syndrome of disseminated intravascular coagu-

lation. Acute multisystemic failure. Sepsis. Septic shock. **Conclusion:** Thus, this case report notifies general practitioners of various localization of tuberculosis. Examination of patients with abdominal tuberculosis demands, first of all, correct interpretation of anamnestic, clinical, laboratory, radiological data and results of special methods of research. A combination of this data is absolutely accessible to any general practitioners where patients are admitted for the first time, it is sufficient for primary selection and further patient's examination to confirm tubercular etiology of disease.

Keywords: intestine tuberculosis, purulent fecal peritonitis, terminal stage, Crohn's disease.

Introduction. Abdominal tuberculosis is characterized by polymorphism of clinical presentation, and sometimes proceeds only with a fever without any symptoms, characteristic for diseases of gastrointestinal tract. The digestive tract is involved in pathological process at any lesion localization. Specific changes seldom confine only intestine, lymph nodes or peritoneum. As a rule, these anatomically connected formations are involved in process almost simultaneously. However lesion symptoms of one organ quite often prevail in the clinical presentation that allows evolving disease in a separate clinical entity. Intestinal process localization can arise at any stage of primary and secondary tuberculosis development. Sometimes it develops as a separate disease in the form of the circumscribed lesion of ileocecal or other part of the intestine [1]. Despite positive tendencies in epidemic tuberculosis situation as a whole, dynamics of extrapulmonary tuberculosis (EPTB) is unstable [3, 5]. Diagnostics of extrapulmonary tuberculosis localizations is difficult, this disease tends to proceed hidden, behind a mask of other pathological processes [2, 3, 4]. Unfortunately, there are no many researches on extrapulmonary forms of tuberculosis that cause late detection, more frequent at incurable stage [4].

Research objective: Description of a clinical case of rare localization of tuberculosis and differential diagnostics with Crohn's disease.

Materials and research methods: we present some data of clinical supervision of the patient with abdominal tuberculosis: infiltration-ulcer tuberculosis of intestine with involvement of iliac and colon (MTB (+), analysis PCR-RV). Tubercular mesadenitis. Extensive miliary dissemination of serous membranes of abdomen, focal generalization in the liver, spleen, in the upper lobe of the right lung (AFB (2 +), luminescent method. Complications of the basic disease: Punching of tubercular ulcers of iliac, cecum and sigmoid guts. Diffused purulent - stool peritonitis.

Results and discussion: Patient A., female, was admitted to «Republic Hospital №2–Emergency Center» in February 19, 2018, at 12.13 p.m., transferred from gastroenterological department of «Yakutsk municipal clinical Hospital» (YMCH) to coloproctological department (CD) with the diagnosis: Crohn's disease with a lesion of cecum, ascending colon, stricturing course, severe case.

Diagnosis on admission: Crohn's disease with a lesion of cecum, ascending colon, active stage. Severe degree. Peritonitis.

Clinical diagnosis: Crohn's disease with a lesion of cecum, small and large intestines. Active stage, severe degree. Perforation of iliac and cecum. Cecum necrosis. Large intestine phlegmon. Diffused purulent-stool peritonitis. A terminal stage. Cachexia. A syndrome of disseminated intravascular coagulation. Acute multisystemic failure. Sepsis. Date of determined clinical diagnosis is February 19, 2018.

Patient's condition at admission: critical: t - 36. 6 C, arterial blood pressure 60/40.

Complaints: stomach ache, general fatigue.

Anamnesis: stomach ache of spastic character started in April 2017, after hirudotherapy course on sterility (transvaginal). In August 2017 the patient was examined in Republic Hospital №1, surgical department. By results of colonoscopy with biopsy, EGD, the diagnosis was: Crohn's disease was confirmed in Moscow, information about the Hospital wasn't known, according to patient's words. She was discharged from National centre of Medicine in November 3, 2017 with recommendations: sulfasan 2 tablets 3 times a day, bifidumbacterin 5 doses 3 times a day during 1 month, nolpaza 40 mg, iron drugs, angoivit 1 tablet 1 time a day. After the discharge, patient was treated by the therapeutist. Analyses showed increase of anaemia, fatigue, periodical pains of spastic character. The patient was hospitalized in central district Hospital in December 11, 2017. Conservative, replaceable haemostatic therapy was made. Anaemia was conserved, occult blood feces analysis +. The consilium with participation of deputy of head physician, deputy of therapeutical department, gynecologist, surgeon-oncologist was in December 18, 2017. The consultation of coloproctologist, colonoscopy was recommended. The patient was hospitalized in coloproctological department from 20.12.17 till 29.12.17. The patient was discharged with amelioration and further treatment at gastroenterologist, surgeon. According to sister's information, exacerbation started in January 2018, liquid stool 5-6 times, bloating, fatigue, no ability to walk. Patient's mother and sister cared for the patient.

The patient was admitted to therapeutic department of central district Hospital and transferred to Yakutsk municipal clinical Hospital for treatment correction. In February 09, 2018 she was Hospitalised in Yakutsk municipal clinical Hospital. Deterioration of health condition began since 16.02.1 with vomiting, bloating, stomach pain in all departments. Abdominal CT was made in February 19, 2018: free air in abdomen. The diagnosis: Crohn's disease with a lesion of cecum and ascending colon, stricturing degree, perforation of a hollow organ. Peritonitis. Cachexia. Anaemia of heavy severity level. The patient was admitted to Republic Hospital№2. After preoperative preparation the patient was operated according to the emergency indications.

Operation course. Date 19.02.2018. Time: the beginning – 14.55, the end - 16.40.

Operation: Subtotal colectomy.

Anaesthetic method: endotracheal anesthesia

Operation course: Median laparotomy under endotracheal anesthesia after processing of operational field by chlorhexidine spirituous solution was done three times. The purulent-fecal exudation with a stinking odour to 2,5 litres, taken to inoculation, was evacuated from abdominal cavity by evacuator. At revision loops of small intestine were bloated with crimson colour in the upper departments, peristalsis was. There was iliac necrosis on a field of 20 cm from iliac-cecal angle and cecum, there were punched foramens in several places on these intestines. A peritoneum in the inferior part was black colour, a big epiploon was necrotized through all its length, rash of whitish, brown, yellow colour from 1 mm to 6 mm on all small and large intestines. Places of necrosis from a serous cover in the dimensions to 5-6 cm in diameter were in large intestine, no peristalsis, large intestine was recognised nonviable from cecum to sigmoid. Mobilisation of mesentery was in 40 cm from iliac-cecal angle to sigmoid gut. Proximal stump (ileac gut) was made. Abdomen was washed by 8 litres of antiseptic solutions. Diffusive bleeding was marked from small pelvis peritoneum. Attempt of hemostasis by electrocoagulation was unsuccessful, imposed by haemostatic sponges, tamponed by 3 napkins, lateral canals, small pelvis was also tightly tamponed by a diaper. Hemostasis. Small pelvis drainage and left lateral canal with

silicone tubes. Nasalintestinal intubation. Sutures were through all layers.

Remote macromedication: large gut with 40 cm of iliac.

Postoperative diagnosis: Crohn's disease with a lesion of large and small intestines. Active stage, severe degree. Perforation of ileac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent - fecal peritonitis. A terminal stage.

The recommendation of the doctor about further tactics of treatment: sanation relaparotomy at stabilization of patient's condition. The early postoperative period was proceeded extremely hard, severe condition of the patient's state was caused by a syndrome of polyorgan insufficiency, DIC syndrome.

19.02.2018 at 20.00. Cardiac arrest happened on the background of the intensive therapy AP 0/0, heart rate 0. Resuscitation actions without effect were within 30 min. Biological death was verified at 20:30.

Postmortem diagnosis.

Basic: Crohn's disease with a lesion of small and large intestines. Active stage, severe degree. Perforation of iliac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent-stool peritonitis. A terminal stage.

Complications of the basic diagnosis: Perforation of iliac and cecum. Cecum necrosis. Large intestine phlegmon. Diffuse purulent-stool peritonitis. A terminal stage. Cachexia. A syndrome of disseminated intravascular coagulation. Acute multisystemic failure. Sepsis. Septic shock.

From the report of pathoanatomical dissecting №118/B from 2/20/2018. (Picture 3, picture 2)

Basic disease: A18.3 infiltration-ulcer tuberculosis of intestine with involvement of iliac and colon (MTB (+), analysis PCR-RV). Tubercular mesadenitis. Extensive miliary dissemination of serous membranes of abdomen, focal generalization in the liver, spleen, in the upper lobe of the right lung (AFB (2 +), luminescent method.

Complications of the basic disease: Punching of tubercular ulcers of iliac, cecum and sigmoid guts. K 67.3 Diffused purulent - stool peritonitis. Operation: Laparatomy, subtotal colectomy, ileum resection in 19.02.2018. D 65 Syndrome of disseminated intravascular coagulation: operational wound bleeding, hemoperitoneum (600 ml of blood and 140 g of red clots). Cachexia (BMI = 12,7 kg/m). Renal - hepatic insufficiency. The general venous anaemia and dystrophic

Fig. 1. Large intestine preparation patient A

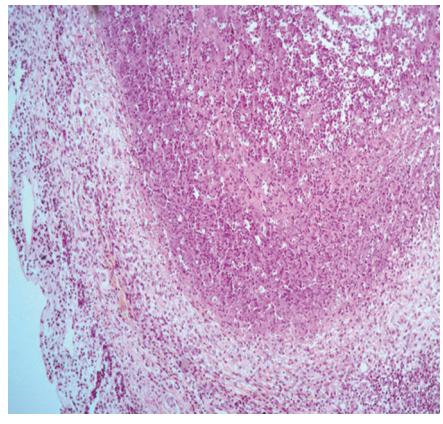

Fig. 2. Colon microscopy patient A

changes of parenchymatous organs. Edema of lungs and brain. A bilateral hydrothorax (left 300 ml, right 600 ml).

Cause of death: K 67.3 Diffuse purulent - fecal peritonitis. D 65 Syndrome of disseminated intravascular coagulation.

The death of the patient was inevitable due to serious diagnosis and extremely critical condition on admission in February 19, 2018.

Conclusion: this case report notifies general practitioners of various localization of tuberculosis. Examination of patients with abdominal tuberculosis demands, first of all, correct interpretation of anamnestic, clinical, laboratory, radiological data and results of special methods of research. A combination of this data is absolutely accessible to any general practitioners where patients are admitted for the first time, it is sufficient for primary selection and further patient's examination to confirm tubercular etiology of disease.

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ECZEMA IN COMBINATION WITH DIPHYLLOBOTHRIASIS IN A REPRESENTATIVE OF ONE OF THE INDIGENOUS PEOPLES OF THE NORTH

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ABSTRACT

The article presents a clinical case of eczema in a representative of one of the indigenous peoples of the North - the Selkup. The disease is associated with professional activity - the collection of wild plants.

The Selkup live in Western Siberia in Krasnoselkupsky district (Russia). They are engaged in reindeer herding, fishing, hunting, gathering and processing of wild plants. Due to the small number and remoteness of their settlements, this ethnic group has not been sufficiently studied. Eczema makes 22% of all skin diseases and other allergic dermatoses in the Selkup population. The incidence of dermatoses in the peoples of the North is closely related to their lifestyle, traditional crafts (reindeer breeding, fishing, gathering of wild-growing plants), as well as impact of adverse climatic factors, and the influence of industrial enterprises on the fragile nature of the North.

The Selkup as typical representatives of the indigenous peoples of the North, leading a traditional way of life are constantly exposed to the adverse effects of the external environment, as well as other health hazards of their professional activity. It is known that eczema is often found in fishermen, reindeer herders and collectors of wild plants.

In the presented clinical case, the patient has a direct link between the exposure to the allergen, in this case, the wild rosemary plant, and the appearance of an allergic reaction in the form of eczema of the right hand and concurrent diphyllobothriasis.

Keywords: Selkup, eczema, diphyllobothriasis, occupational diseases.

Eczema as an allergic reaction of a delayed type is often the result of prolonged contact with various allergens, including professional ones [1].

Health of the North indigenous peoples in recent years is becoming increasingly important due to the significant increase in the development of natural resources in the Arctic and subarctic regions of the country.

The dermatoses' morbidity of the North peoples is closely related to their lifestyle, traditional crafts (reindeer breeding, fishing, gathering of wild plants), the impact of adverse climatic factors, and the influence of industrial enterprises on the fragile nature of the North. Attempts to change the traditional way of life of aboriginal people by resettling them in cities and towns led to an increase in alcoholism, obesity and other burden of urbanization. Of particular importance are the climatic conditions [3].

The factors determining the characteristic features of the climate of Yamal are the long periods of the polar day and the polar night, which form the features of environmental management in the region, as well as affect the radiation balance and its components. The duration of light days increases the influx of total annual solar radiation [3].

Along with the problem of anthropogenic and technogenic pollution of the environment, most of the regions of the North also have the problem of the wide distribution of various biogeochemical anomalies, among which the leading place belongs to the natural iodine deficiency and widespread iodine deficiency diseases [3].

The Selkup live in Western Siberia in Krasnoselkupsky district. They are engaged in reindeer herding, fishing, hunting, gathering and processing of wild plants. Due to the small number and remoteness of their settlements, this ethnic group has not been sufficiently studied. Eczema makes 22% of all skin diseases and other allergic dermatoses in Selkups population [3].

The Selkup as typical representatives of the indigenous peoples of the North, leading a traditional way of life, are constantly exposed to the adverse effects of the external environment, as well as other health hazards of their professional activity. It is known that eczema is often found in fishermen, reindeer herders, and collectors of wild plants [2]. We present a case of eczema in Selkup, which was caused by exposition to various environmental factors as well as diphyllobothriasis.

Patient K., 69 years old, male, presented to consultation room with complaints of an itchy rash on his hands, frequent headaches, shortness of breath on exertion, cough with mucous sputum, chest pain, belching, abdominal pain, mainly in the epigastric region and general weakness. The patient was admitted to therapeutic department of the Tarko-Salinsky Central Regional Hospital for further evaluation and treatment. K. was born in Krasnoselkupsky District and he lived for 25 years in a chum (in Siberia and in the northeast of the European part of Russia: a portable dwelling in the form of a tent of conical shape, covered with skins, bark, felt, etc.). He was a reindeer herder, a collector of wild medicinal plants (wild rosemary, lingonberry, etc.). Patient's history was remarkable for scabies which was treated with home remedies, pyoderma (probably caused by a dirty sewing needle) which was assessed and managed by shaman. Reindeers were present at patient's environment. Patient's home was infested by cockroaches and bedbugs. He had allergic reactions to bedbug bites periodically.

At the time of presentation, patient lived in a comfortable apartment in Krasnoselkup, unemployed. Patient is married and has 8 children living in the city of Tarko-Sale. Hereditary history - parents suffered from cardiovascular pathology and chronic obstructive pulmonary disease (COPD). He denies surgery, injuries. First symptoms of eczema appeared more than 10 years ago, when patient noted rash on the hands during collection and processing of wild rosemary. Patient visited shaman for the treatment of these symptoms. .

In 2014, patient visited an epidemiologist who put the diagnosis of diphyllobothriasis, chronic phase. Additionally patient had severe COPD, bronchectatic disease, respiratory failure, 2 degree, chronic cholecystitis and pancreatitis in remission. Following recommendations were given – strict adherence to diet, choleretic herbs, hofitol 1 tablet tid for 14 days, vitamins, observation by an infectious disease specialist at the place of residence.

Physical examination: The general

condition of patient is satisfactory, patient is alert and responsive. Pharynx is calm. Visible mucous membranes are clean. Peripheral lymph nodes are not enlarged. Osteo-muscular features are unremarkable. The chest is symmetrical, both halves are involved in breathing. Percussion sound over lungs is pulmonary. Harsh breathing on both sides, isolated dry rales. Respiratory rate is 19 per min. Heart sounds are muffled and rhythmic. Heart rate is 68 per min. BP 160/90 mmHg. Tongue appears wet, clean. The abdomen is flat involved in breathing and not tender or rigid. Liver is at the edge of the ribcage. The spleen is not enlarged. Bowel movement is regular. No costavertebral angle tenderness. Urination is regular and painless. Peripheral edema is absent.

Skin is of physiological coloration, hydration and tissue turgor are normal. Eczema was asymmetric involving only right hand. It was presented by pathological elements in the form of a papule-vesicular elements, pink in color, with serous content, and weeping with moderate erythema; focal, large-peeling white flakes located on the back of the right hand.

Laboratory data: complete blood count on July 16, 2014 - RBC 4.87, hemoglobin 132 g/l, platelets 301*10/l, WBC .4810/l, eosinophils 1%, nuclear neutrophils 1%, segmented neutrophils 56 %, lymphocytes 37%, monocytes 5%, ESR 8 mm/h. Biochemical analysis of blood on 10.07.2014: prothrombin index 88%, AST 23 U/l, ALT 17 U/l, bilirubin 10.6 μm/l, creatinine 59 μm/l, cholesterol 4.4 mm/l, total protein 78 g/l, sugar 4.2 mm/l. Urinalysis on July 16, 2014 color is yellow, specific gravity is 1010, pH 5.5, transparent, glucose negative, protein negative, leukocytes are 0-1 in sight, few epithelium in sight. Helmnitoses on 07/16/2014: not found. Syphilis on 07/16/14 - negative. Microscopy of skin scales for pathogenic fungi – negative on 3 samples.

Echocardiography on 07/30/2014: Echo-signs of aortic atherosclerosis. Dilatation of the left ventricle. Left ventricular hypertrophy. Mild atrioventricular valvular insufficiency. Atrial septum aneurysm, type A (without PFO).

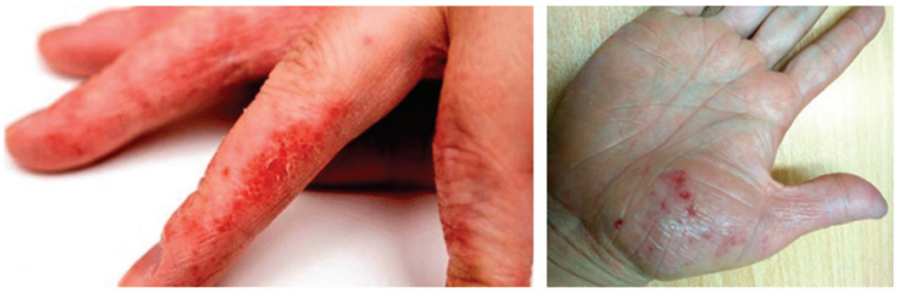

Fig. 1 (a, b). Patient, 69 y.o. Eczema of the hands.

Abdominal ultrasound scan on 07/03/2014 - The size and structure of the liver is not changed. Slight torsion of gallbladder neck. Increased echogenicity of pancreatic tissue. Suspected small calculus in the left kidney.

Based on complaints, medical history and physical examination, a diagnosis was made: Ischemic heart disease. Angina pectoris, functional class (FC) 2. Arterial hypertension III, cardiovascular risk category 4. Chronic pulmonary heart. Chronic heart failure 1. FC 2. Severe COPD, stage of incomplete remission. Left-sided bronchiectasis, respiratory failure 2nd degree. Chronic cholecystitis, pancreatitis, in remission. Diphyllobothriasis, chronic phase. Eczema of the right hand (Fig.1, a, b).

Treatment: infusion therapy, a polarizing mixture, heparin, aminophylline, amlodipine, levofloxacin, spironolactone, indapamide, aspirine, vitamin therapy, inhalation of ipratropium bromide and fenoterol mixture (Berodual®), suprastin, locally compounded ointment of betamethasone, gentamicin and clotrimazole (Akriderm GK®) bid, application of Fucorcin® 2 times a day with a positive effect.

Patient was discharged with recommendation of observation of a district therapist, a dermatologist, an infectious disease specialist, avoidance of contact with the plant (wild rosemary), to continue taking Indapamide 2.5 mg in the morning, Amlodipine 5 mg 1 tablet 2 times a day continuously.

Conclusion. Thus, in this patient, having a history of diphyllobothriasis in the chronic phase, a direct link was found between the influence of the allergen, in this case the wild rosemary plant, and the appearance of an allergic reaction in the form of eczema of the right hand.

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EXPERIENCE EXCHANGE

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PSYCHOEMOTIONAL STATE AND CONDITION OF THE VEGETATIVE NERVOUS SYSTEM OF ADOLESCENTS IN YAKUTSK

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ABSTRACT

The article is devoted to the topical issue in pediatrics – the assessment of adolescents' psychoemotional state and condition of the autonomic nervous system. It is known that vegetative dysfunction and psychoemotional condition are the basis for formation of such widespread socially significant diseases as arterial hypertension, bronchial asthma, pathology of gastrointestinal tract, which require correction of autonomic homeostasis.

Goal of the research is to study psychoemotional state and condition of adolescents' autonomic nervous system. Authors present their work on the study of 300 adolescents at the age of 15, students of secondary schools in Yakutsk. Assessment of social adaptation and autonomic stability nature was carried out on Gavlinova's questionnaire. Neuropsychological methods of Eysenck, Spielbergerand Leonhard were used to determine psychoemotional status. The variability of heart rate was studied by using the Cardio Expert computer of cardiointervalographic system.

Results of the study allowed describing the psychoemotional state and personality traits of adolescents. The teenagers are mostly extrovert or potential extroverts, and they are characterized by a high level of anxiety. Hyperthymic, affective-exalted, emotive and cyclothymic types of accentuations prevail among adolescents.

The majority of adolescents have an average level of social adaptation and vegetative resistance. Low social adaptation and low vegetative stability are most often observed in young men.

Obtained results showed that the imbalance of autonomic nervous system is present in adolescents of both sexes. Sympaticotonia, functional tension and overstrain, an increased response of the cardiovascular system to an orthostatic test, excessive, inadequate and paradoxical vegetative maintenance are characteristics of adolescents. Unsatisfactory adaptation in adolescents is often observed. Adolescents are at risk of developing psychosomatic pathology, and therefore they need regular follow-up and preventive care. The results make it possible to recommend cardiointervalography for all adolescents.

Keywords: adolescent, health, psychoemotional state, autonomic nervous system, cardiointervalography.

At present, there is much concern about the problems of preservation and strengthening the health of adolescents in Russia [10]. There are 11 293 thousand children aged 10-17 years at the beginning of 2017 in Russia. It is 8.1% of total population of the country. Indicators characterizing theincidence of adolescents, especially 15-17 years old, remain disappointing [7, 10]. At this age, the body of adolescents is very sensitive and unstable to high training loads and emotional stress.

Autonomic dysfunction is the basis of many neurotic and psychosomatic disorders among adolescents. The prevalence of this state increases with age, and it reaches 65-72% in the adolescent population [5]. It is well known that vegetative dysfunction is the basis for formation of such widespread socially significant diseases as arterial hypertension, bronchial asthma, pathology of gastrointestinal tract, which require complex rehabilitation. This rehabilitation also optimizes vegetative homeostasis [7].

The psychoemotional state of adolescent takes an important part in assessing the health condition. Psychoemotional factor should be considered as a master factor of human health andas the main component of psychological diseaseprevention. Currently, problem of studying the factors that may contribute to the health of today's adolescents is particularly relevant.

Objective of our research is to study the psychoemotional state and condition of the autonomic nervous system of adolescents at the age of 15.

Study materials and methods. Examination of 300 adolescents at the age of 15, living in Yakutsk, was conducted in the course of the work.We used the adapted personal two-factor questionnaire of M. Gavlinovato assess the adaptation of adolescents. This questionnaireis based on the use of two scales, which are social adaptation and autonomic stability.Neuropsychological methods of Eysenck, Spielberger and Leonhard were used to determine the psychoemotional state and personality traits.The variability of heart rate was studied by using the Cardio Expert computer of cardiointervalographic system.

Results and discussion. Assessment of the adolescents'psychoemotional health is one of the most important characteristics of health condition. The study of personality traits allowed to determine the severity of factors extroversion /introversion and neuroticism / emotional stability in adolescents. According to the test of Eysenck,extroversion-introversion is 14.25 ± 0.7 (max - 24 points), neuroticism-emotional stability is 10.42 ± 0.69 (max - 24 points).

Introverts and potential introverts are only 10%, ambiverts are 18% among adolescents.Extroverts and potential extroverts account for 72% among adolescents.

Thus, today's young people are mainly extroverts. They are characterized by attitude toward the world around them, by impulsiveness, initiative, sociability, behavioral flection, aspiration for contacts and new impressions. The adolescents are also characterized by uninhibited forms of behavior, high motor and speech activity [9].

Anxiety factor is among the important psychological components of personality. The study of anxiety in adolescents was carried out by using the questionnaire of C.D. Spielberger.It showed that adolescents with a high and medium-high level of anxiety are 49.0%.The average level of anxiety indicators among girls is 14,78 ± 1,3 and young men is 18,92 ± 1,5.

The peculiarities of character accentuations were studied with the help of the Leonhard'smethod during psychological research.Analysis of

Table 1

Indicators of adolescents' cardiointervalometry

	Girls	Boys
Variationalrange (X, sec)	0,25±0,01	0,21±0,01
Averageinterval (M, sec)	0,79±0,01	0,74±0,01
Mode (sec)	0,78±0,01	0,74±0,01
Mode amplitude (%)	43,64±1,38	48,23±1,36
Stress index (c.u.)	161,77±17,9	166,29±21,2
Heart Rate, sec	77,7±0,99	82,34±0,85
SDNN, sec	0,052±0,002	0,044±0,001
RMSSD, sec	0,050±0,003	0,038±0,001

Table 2

Indicators of spectral analysis

	Girls	Boys
HF	1070,62±157,03	718,20±124,85
LF	2842,06±514,10	3045,29±326,90
VLF	2874,80±446,80	3683,10±461,31
LF/HF	2,38±0,16	3,26±0,35
LF,%	62,67±1,35	68,20±1,13
HF,%	35,32±1,35	30,77±1,43
TF	4459,4±407,0	5037,2±1225,7

the results showed that adolescents predominate in the hypertensive - 0,69 ± 0,1, affectively-exalted - 0,65 ± 0,09, emotive - 0,63 ± 0,1 and cyclotimous types - 0,62 ± 0, 09.

Adolescents are characterized by manifestation of exaltation, impressionability, strong attachment to friends and companies. They easily can be fascinated by joyful events andfall unto despair by sad things.It creates the ground for social maladjustment,the risk of alcoholization and narcotization of a teenager [8].

The study of the autonomic nervous system's functional stateis important for determining the level of adolescents' health from position of organism's adaptive capabilities.

Results of the survey on determination of social adaptation and autonomic resistance showed that 77.8% of girls and 67.1% of boys had an average level of social adaptation. A high level of social adaptability is observed in 7.8% of girls and in 8.7% of young men. Low social adaptation is most often observed in young men - 24, 2% and in girls - 14.7%.

The results'analysis of the vegetative stability's determination showed that the average level of vegetative resistance is in 60.8% of girls and 53.0% of young men. 25.5% of girls and 25.6% of young men have a high level of vegetative resistance. Low vegetative stability is most often observed among young men - 21.4%, among girls - 13.7%.

The autonomic nervous system ensures maintenance of homeostasis and normal regulation of the activity of all organs and body systems [1]. In this case, the cardiovascular system is one of the most responsive to changes in the body's balance with the environment [6]. It is cardiovascular system is considered as a universal indicator of all pathological processes, reflecting the state of regulatory mechanisms and adaptive capabilities of the organism [1, 2]. The main indicators of cardiointervalometry were analyzed in the course of the study: variation range intervals (X, sec), average interval (M, sec), mode (MO, sec), mode amplitude (AMO, %), index of regulatory systems tension (IT, conditional unit).

Determination of the initial vegetative tone in adolescents of different sex's revealed differences. Vagotonia is most common among girls - 27.2%, among boys - 16.3%. Accordingly, eutonia is registered equally often among girls and boys, 27.2% and 27.5%. Sympathicotonia most frequently registered among boys - 56.3%, girls - 45.2%. Table 1 presents the main parameters of cardiointervalometry obtained in the examination of adolescents.

Index of the variational range in adolescents (> 0.30) corresponds to normotonia. The mode amplitude (31-49 in the normal condition) and stress index (51-199 in the normal condition) do not exceed the limits of normotonia. However, their increase was observed among boys in comparison with girls. It reflectsthe increase in sympathetic regulation, strain of the system functioning and confirms the predominance of sympathicotonia in young men. Relatively high MO in representatives of both sexes showed a high level of humoral factors'influence. Such mechanisms of heart regulation are imperfect, and it represents a danger of overstress and disruption of adaptation [3, 11].

The maximum value of SDNN (standard deviation) is -0.048, the value of RMSSD is 0.045. Thus, we can talk about reducing parasympathetic activity of adolescents.

Parameters of spectral analysis of heart rate variability in adolescents were also examined. Results are shown in Table 2.

Analysis of the results showed that the value of high-frequency spectrum (HF 0.15-, 4 Hz), reflecting respiratory arrhythmia and vagal control of the heart rhythm, is higher among girls - 1070.62 ± 157.03 than among boys - 718.20 ± 124, 85.Calculated component oflow-frequency oscillations index (LF 0.04-0.15 Hz), which has mixed origin and associated with both vagal and sympathetic cardiac rhythm control, is higher among young men - 3045.29.

The value of VLF (power of ultra-low frequency heart rate fluctuations <0.04 Hz), reflecting the activity of the suprasegmental level of the VNS, is higher amongboys - 3683.10.

Thus, according to cardiorhythmography, adolescents have high level of cardiac rhythm control's centralization, relatively high level of activity in the sympathetic department of the autonomic nervous system and low rates of parasympathetic activity in the autonomic nervous system.

Activity index of regulatory systems (PARS = AMO / Mo) allows to estimate the degree of functional tension and overstrain in adolescents. We found that functional tension is observed in 29.4% of adolescents, they are characterized by a lack of protective and adaptive mechanisms, an inability to respond adequately to environmental factors [3, 4].

Functional reserves of adolescents' body were determined taking into account the dynamics of heart rate variability parameters during the exercise test (an active orthostatic test).

Adequate response of the cardiovascular system to orthostatic test is determined in 63.4% of adolescents, increased and significantly increased response is determined in 25.6%.

According to the consistency of changes in the static parameters MxDMn and AMo, diagnostic algorithm of our program evaluates the vegetative support.Sufficient vegetative maintenance is found only in 37.4% of adolescents, excessive and extremely excessive provision is found in 38.1%, insufficient provision in 9.9%, paradoxical provision in 14.6%.

According to results of the Cardio Expert computer of cardiointervalographic system, satisfactory adaptation is observed in 43.6% of adolescents, the tension of adaptation mechanisms is 40.9%, unsatisfactory adaptation is 15.5%.

Conclusion. Results of the study allowed characterizing the psychoemotional state and personality traits of adolescents. It was revealed that adolescents are mostly extrovert or potential extroverts. A high level of anxiety is typical for them. Hypertensive, affective-exalted, emotive and cyclotimous types of accentuations prevail among adolescents.

Evaluation of social adaptation's nature and autonomic stability showed that most adolescents have an average level of social adaptation and autonomic resistance.Low social adaptation and low automatic stability are most often observed in young men.

According to cardiorhythmography, adolescents have a high level of cardiac rhythm control'scentralization, relatively high level of activity in the sympathetic department of the autonomic nervous system and low rates of parasympathetic activity in the autonomic nervous system.

Sympathicotonia occurs much more frequently among boys than among girls. Apparently, the young men experiencea change in social circumstances more emotionally and continuously.

Thus, the obtained data showed that imbalance of the autonomic nervous system is present in adolescents of both sexes.Adolescents are at risk of developing psychosomatic pathology in the future and therefore they need regular follow-up and preventive measures. Sympaticotonia, functional tension and overstrain, increased cardiovascular system response to an orthostatic test, excessive, insufficientand paradoxical autonomic maintenance are characteristic of adolescents.The obtainedresults make it possible to recommend cardiorhythmography for all adolescents.

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PROBABLE CAUSES OF VILYUI ENCEPHALOMYELITIS. FACTS OF THE HISTORY OF STUDY AND REASONING

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ABSTRACT

Vilyui encephalomyelitis (VEM) is a degenerative disease of the central nervous system, in acute form, manifested by meningoencephalitis, which ultimately tends to develop in the form of long-term chronic progressive panencephalitis. Rapidly progressive cases of the type of fatal slow infection lead the patient to death ranging from 2 months to 6 years. We have developed a new hypothesis about the anthropozoonotic nature of the disease, based on an analysis of the sudden stop of the incidence of VEM.

The **purpose** of this article is to provide a scientific basis for this hypothesis. We analyzed extensive data from clinical observations of VEM patients, according to archive data stored at the former NEFU Health Research Institute, as well as a review of scientific publications on VEM over the past 30 years. A long-term study of VEM demonstrated the validity of the infectious hypothesis VEM. However, when considering possible causes, detailed studies were not conducted due to the detection of antibodies in several different candidate viruses in small, statistically unreliable groups of patients. The putative etiological agent was not reliably isolated. Attempts to infect various laboratory animals were not successful. Clinical and epidemiological data indicated the likelihood of horizontal transmission of the suspected pathogen from person to person. We compared the dynamics of the VEM epidemic process and found that the time of the disappearance of its epidemics coincides with the period of disappearance of some species of rodents and birds, potential carriers of the VEM virus in biocenosis. This allows us to return to the assumption of the primary anthropozoonotic nature of the disease. It is not excluded that the epidemiological chain, broken by the current epizootics, can be revived in the context of the active introduction of modern man into the environment.

Keywords and abbreviations: Vilyui encephalomyelitis (VEM); Infectious hypothesis; Anthropozoonoses; Epizootic; Epidemiological chain; Biocenosis; Vilyuisk Human Encephalomyelitis virus (VHEV); Theiler-like virus; Theiler murine encephalomyelitis virus (TMEV); Bornavirus; California Virus encephalitis (Bunyaviridae); Viruses of Eastern and Western equine encephalitis (Alphavirus); the Virus encephalitis San Louis (Flavivirus); Immunoglobulinum G (IgG); Cerebrospinal fluid (CSF).

Introduction. For more than 60 years of study of Vilyui encephalomyelitis (VEM), the disease was reliably registered only in the indigenous population of Yakutia (Sakha, Evens, Evenks), mainly living in remote and sparsely populated rural areas. In archival sources, materials of isolated cases of probable VEM of people of another ethnic group (mostly Russian or mestizo) are available for discussion. Often Vilyui encephalomyelitis starts with high temperature (39-40°), chills, painful headache, muscle aches and extreme fatigue. In chronic form, progressive dementia, speech disorder, lack of facial expressions, violation of motor function prevail. In severe progressive cases, the disease leads to death within 3-5 years [7].

In the monograph "Vilyui encephalomyelitis" [2] summarizes the main achievements in the study of VEM. It is indicated that the main reason for the nomination of several mutually exclusive or partially interfering hypotheses about the origin and pathogenesis of VEM is the uncertainty and often incomplete results of studies that could potentially fully confirm or refute the assumptions. "Each hypothesis was proposed by bright authoritative scientists who did not have a great desire to listen to opposing opinions or work in a direction that would allow to refute their own hypothesis. Therefore, the discussion of the 1970-ies, whatever they may be interesting, has not led to the solution of the problem." But most importantly, the causative agent of VEM is not isolated. In accordance with the latest research in the field of pathogenesis of VEM and other chronic inflammatory diseases of the Central nervous system, immunopathological mechanisms were identified, which apparently play a crucial role in the development and maintenance of a long inflammatory process. "Detection of intrathecal production of oligoclonal IgG, which is consistently present for 3 decades after the onset of the disease in the subacute and early stages of the chronic phase, i.e. at a time when the inflammatory process is still active [5,20], as well as the Association between VEM and rare variants in the IFN-G gene [14] and the probable role of *IFN-G* in the pathogenesis [2, 14] characterize VEM as a disease with a pronounced immunopathological component. This leaves the assumption that an infectious agent causes destruction of neurons on the background of insufficiency of the immune system, most likely. Research in this direction should be continued" [2]. Over the year, 26352 patients are hospitalized with encephalitis in the USA, of which 49.7% of the etiology of the disease remains unspecified [15]. In the Russian Federation, from 15,000 to 32,000 patients with inflammatory diseases of the central nervous system, including in Yakutia, from 50 to 80 cases, almost all of them can be considered cases with unexplained etiology. Searches of candidate viruses among patients with encephalitis with an unclear etiology, while also being an unexplored problem, by no means eliminate the problem of Viluy encephalomyelitis from this list.

Materials and methods of the research. We analyzed the current state of the VEM problem in the available literature and materials of the archival database of the former Scientific-Research Health Institute of NEFU, including patient histories, reports of clinical and epidemiological observations since the 1960s, focusing on the following main areas of research: epidemiology, etiology, pathogenesis and features clinical manifestations.

Discussion. Based on the results of epidemiological studies conducted under the direction of L. G. Goldfarb, chief international coordinator of long-term VEM studies, it was shown with sufficient conviction that VEM is an infectious disease resembling slow infections.

This is indicated by the following scientific facts:

1. The nature of the spread and extinction of the disease [13], characterized by a marked evolution in the clinical picture of the disease from predominantly acute and subacute forms to predominantly long-current chronic forms, the spread of the disease first from the left Bank to the right Bank settlements of the Vilyui district and then to Central Yakutia, the disappearance of VEM from the Central.
2. Predominantly young age of patients - 30-34 years.
3. The spread of the disease

through migrants during the period of increasing morbidity in the 1960s - 1970s. According to N.I. Fedorova et al. [2] foci of VEM in some villages of Central Yakutia are formed around immigrants coming from high-risk areas, mainly Vilyui and Kobyai.

4. Aggregation of patients in families is equally common for families with sick blood relatives, and for families with sick adoptive relatives [2].

5. The case of the fatal disease of a laboratory assistant of European ethnicity after making herself a subcutaneous injection of the VEM patient's serum for suicidal purposes. The case of VEM was clinically confirmed by D.K. Gaidusek [17], the autopsy revealed morphological pattern between multiple sclerosis (MS) and VEM.

6. Aggravation of clinical manifestations of the disease in the case of secondary morbidity (for example, in families), reminiscent of the phenomenon of increased virulence in subsequent passages in the experiment [2].

7. Not a blood relatives and non-relatives cases of VEM in some families with prolonged household contact (a vivid example – a family of the VEM patient S.: his first wife became ill and died from VEM at the age of 37 years, and his second wife after his death 5 years later, also became ill and died from VEM 2 more women who had an extramarital affair with this man and 2 men colleagues (archives of the SR Institute of Health, NEFU, Yakutsk).

8. L. G. Goldfarb et.al, explained the seasonal distribution of the disease manifestation in the spring and autumn by the seasonal increase in agricultural work (plowing, hay harvesting, etc.) [2]. However, we would like to note that the highest incidence is observed in May. At this time, the village is not carried out massive agricultural work, but begins the spring hunting for waterfowl (May – for migratory ducks, June –for Turpan). The autumn peak of the disease August-September also coincides with the period of reduction of agricultural work and autumn duck hunting (August) and hares (September). According to the Yakut tradition, men hunt and women cut the prey, this fact is probably one of the main reasons for the high incidence of women in the initial stage of the VEM epidemic.

9. The difference in the number of sick men and women during the period of increase and decline in the incidence of VEM: the predominance of women in the first period and the equalization of the gender difference in the second period of morbidity [2], also, in our opinion, it is most likely due to a change in the predominant ways of transmission. In the first period, the transmission of infection probably occurred when cutting the carcasses of infected animals, and in the second - household way from a sick person to a healthy one.

The search for the causes of the disease revealed in the serum of patients with VEM antibodies against a variety of infectious agents. In discussing these issues, we came to the conclusion about the selection of candidates for an infectious agent of VEM and decided to include in this list the following viruses: Vilyuisk Human Encephalomyelitis virus (VHEV); Theiler-like virus (TMEV); Bornavirus; California Virus encephalitis (Bunyaviridae); Viruses of Eastern and Western equine encephalitis (Alphavirus); the Virus encephalitis San Louis (Flavivirus) [2]. Our experience in studying the causes of VEM and literature analysis suggests the following ways of transmission:

- Vector-borne: arthropod Diptera (mosquitoes), ticks, fleas, lice, bugs. The existence of a vector-borne route of transmission allow you to suspect the findings of antibodies to the causative agents of encephalitis, is transmitted by these viruses: California encephalitis (Bunyaviridae), Eastern and Western equine encephalitis (Alphavirus), encephalitis San Louis (Flavivirus);
- Contact: long household contact (blood, saliva?), sexual ("some village epidemics" according to clinical and epidemiological observations).
- Parenteral: blood transfusion. For example, patient P., from village Dalyr, Ust-Aldan, dates of birth and death 1955 -1993, the onset of the acute VEM in November 1984, but 6 months before the disease he had got a blood transfusion because of a serious knife wound. Manifestation of VEM with fever, meningeal symptoms, psychotic disorders, coma, (in liquor protein 330 mg/l, lymphocytic cytosis 27 cells) stage of intermission after acute VEM lasted 5 months. After that, the exacerbation of the disease manifested in the form of subacute VEM with the rapid development of a typical clinical syndrome with dementia, spastic tetraparesis, dysarthria. The duration of the disease was 9 years (Archive of SR Health Institute, NEFU, Yakutsk).

The spectrum of antiviral antibodies in the serum of patients with VEM allows one to suspect involvement in the development of the disease by a zooanthropic infection transmitted through the blood, probably by contact or transmission. We found a coincidence of the peak incidence and disappearance of the epidemic outbreak of VEM in Yakutia with the disappearance of the common rodent form of *Arvicola terrestris* and the local population of migratory ducks, *Anas formosa*, the main prey of spring hunting of the local population, and the elimination of malaria in Yakutia.

Arvicola terrestris

This animal disappeared on the territory of Yakutia in the early 1990s for an unknown reason. Epizootics is not excluded. *Water (Field) vole* was widespread and was numerous throughout Russia. In Soviet times, people hunted up to 5 million skins of *Field voles* per year [5]. Until the middle of the XVIII century *Arvicola terrestris* served as a delicacy of the indigenous population [1] and this custom was eradicated in connection with the adoption of Christianity. The students were engaged in hunting on these animals, some champions for the season were mined up to 1000 skins. Rodents have had daring temper and often bite the young hunters. Of course, most of the mothers and sisters helped to remove the skin of the rodent. The prevalence of the species in Yakutia has been declining since the 1980's. "The number of *Water voles* in the last 20 years are very low, the last time we caught them in the Lena district in 2002, also they appeared in the vicinity of Yakutsk . Residential burrows were found in the autumn of 2017, but no animal could be caught. Also there were noted traces of stay in the Amginsky district in July 2018" as it known from personal message of Candidate of Biology O.I. Nikiforov. "In the vicinity of Yakutsk for 20 years did not come across a *Water vole*. I with students in recent times caught them in about 1995. The decrease in its population, with occasional appearance in some regions observed throughout Russia. For *Water voles* have established a clear link with tularemia" – private message from Doctor of Biology E.G. Shadrina. *Arvicola terrestris* is a reservoir of the following infections: tularemia, Omsk hemorrhagic fever, leptospirosis, some vector-borne infections, etc. In addition, in the 1980s., *Field mice* in the homes of villagers began to be replaced by *House mice* due to the mass importation of animal feed.

Elimination of malaria. The fight against malarial mosquitoes in Yakutia was launched malarial stations, organized for the first time in 1936. The 1964th is the year of eradication of malaria in Yakutia [9]. Antibodies against malarial Plasmodium (weakly positive) were found in 100% of the examined patients with VEM. On the other hand, according to clinical and epidemiological studies,

only three patients with VEM suffered from malaria [2]. *Isn't the resistance to malaria a predisposing factor of VEM? This hypothesis should also be tested.*

The etiology of VEM

Attempts to isolate the infectious agent by inoculation of biological material of patients with VEM were not successful. Two successful attempts to isolate infectious agents E.S. Sarmanova et al. [8] and A.S. Karavanov et al. [3] up to the present time have not been recognized as the cause of VEM.

What is the cause of failure? We see three reasons for this (from the standpoint of the infectious nature of the disease):

1. Perhaps, materials from the patients inoculated experimental animals did not contain the virus, due to the fact that the replication of the virus occurs only in the acute period of the disease, when fever. The Human organism is likely to rapidly eliminate the virus, but the further development of the disease is supported by unknown infectious virus molecules, probably incorporated into the genome of infected cells of the patient, or as in the case of the experimental model of TMEV infection, the virus persistence persists in very low titers [18];
2. There is a possibility of having another mechanism of the infection. In the case of VEM, we are dealing with a completely new, previously unknown mechanism of transmission of an infectious agent, and the infectious agent is a previously unknown molecule or agent of protein nature;
3. Only Homo sapiens can be susceptible to the virus.

Over 60 years of study history of VEM, the efforts of an international group of researchers have been directed to the search for an infectious agent in accordance with Koch's postulates. It should be noted that D.K. Gaidushek and B. Marshall with R. Warren received the Nobel Prizes, proving the infectious nature of the Kuru and gastritis in accordance with Koch's postulates. But in the case of VEM, these postulates do not work. In our opinion, the fact that the main contender for the cause of VEM HMEV has a special weapon in the form of unstructured protein L * draws attention to itself. But articles appeared in a number of reputable international publications confirming the contaminant nature of the HMEV virus [12]. After these reports, all studies in the world on this virus were probably discontinued, but the Russian virologist, prof. G.G. Karganova isolated a new virus from the canned same material E.S. Sarmanova [6]. According to the RNA sequences, this virus differs from HMEV (G.G. Karganova's personal communication). We had very good reasons to check the Taylor-like viruses for the etiology of VEM. It should be noted that, until now, metagenomic studies, analysis of the degree of DNA methylation, sequencing of RNA, full-genome sequencing of DNA, mtDNA and identification of proteins in the brain tissue of a patient with VEM have not been studied. The exomic sequencing of the genome of VEM patients in the USA and in Russia did not yield breakthrough results [2]. In addition, studies to determine the antigenic specificity of oligoclonal IgG CSF in patients with VEM with antigens of candidate viruses have also not been conducted.

Conclusion. There is compelling clinical, pathological, and epidemiological evidence that VEM is a contagious infectious disease with a prevalent pattern of latent and chronic infections. The intensive search for the infectious agent VEM has not been crowned with success, but the possibilities of finding the causes of VEM using modern research methods have not been exhausted.

In this paper, we put forward an assumption about the anthropozoonous nature of the disease, it is assumed that under the guise of VEM can manifest clinically similar neuroinfections caused by a number of previously undetected viruses in the region, carriers of which can be some animals and birds of biocenosis.

The following rodents and mammals may be likely intermediate hosts of VEM candidate viruses: medium shrew *(Sorex caecutiens)*, water vole *(Arvicola terrestris)*, house mouse *(Mus musculus)*, field mouse *(Apodemus agrarius)*, Siberian chipmunk *(Tamilas sibricus)*, ermine *(Mustela erminea)*, weasel *(Mustela nivalis)*, squirrel *(Sciurus)*, hare white *(Lepus timidus)*. From migratory ducks: pintail *(Anas acuta)*, Siberian turpan *(Melanitta fusca stejnegeri)*, teal cloctoon *(Anas formosa)*. The choice of species for the study was made on the basis of the following criteria: they are reliably established reservoirs of candidate viruses, are related to the economic activities of the population of endemic VEM areas, or migratory birds from regions where VEM candidates are registered. Mice and water voles are TMEV reservoirs, but on the territory of Yakutia which Taylor strains of such viruses circulate is not known. Water vole and chipmunk were the subject of hunting until the 60s. and animal skins were harvested by Rural Consumer Society units. Ermine and squirrel up to the present are hunting animals. Weasel and ermine feed on voles, so their probability to be a TMEV reservoir is high. The literature describes three deaths of people infected with Born virus from a variegated squirrel in Germany [19]. In Alaska, strains of California encephalitis have been isolated from hares, and antibodies to the virus have been isolated from Indians [11, 16]. From the rodent the medium shrew has been isolated of a Hunt virus called the Lena river virus (LNAV), but its role in human disease has not been elucidated [21]. Of migratory ducks, the *Anas Formosa* wintering grounds are China, Japan, and Korea, where cases of human occurrence of California and Japanese encephalitis are recorded, the Siberian turpan also overwinter in these places. The most common and highly migratory duck is the pintail. She is found everywhere. It is known that it flies to India and other countries of Southeast Asia for wintering, including Sri Lanka and Borneo, which is probably why this duck can bring the viruses Eastern and Western equine encephalitis, and St. Louis encephalitis to East Yakutia. In addition to the California encephalitis virus, the Syr-Daryinsky virus and other Taylor-like viruses in the territory of Northern Eurasia, the VEM candidate viruses were not registered [21]. In connection with the above, the search for these viruses for the first time can ascertain the natural foci of their circulation, which is of not only theoretical but also practical importance for the prevention of diseases caused by these viruses.

Thus, funding research on clarifying the circulation of VEM candidate viruses and similar neuroinfections in zoonotic foci of a region that is endemic in VEM is an urgent problem for Yakutia. Such work will undoubtedly play a significant role in ensuring the biological safety of the Russian Federation.

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The authors deny the emergence of conflict in the course of the study.

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