Practice Oriented Science:
UAE – RUSSIA – INDIA

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CIRCADIAN RHYTHM OF TOTAL PERIPHERAL VASCULAR RESISTANCE IN SEVERE CONCOMITANT TRAUMATIC BRAIN INJURY IN CHILDREN OLDER THAN 7 YEARS

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Abstract. *The indicators of a comprehensive examination of 36 patients of school age (7-18 years old) with severe concomitant traumatic brain injury (SCTBI) were studied. On day 1, the mesor of the circadian rhythm GPVR in groups 1 and 3 did not differ from the normative limits, while in group 2 an increase of 60% was noted. It was revealed that the GPVR values in children of the 3rd group were higher than in the 1st and 2nd groups to a greater extent during the day (at 8, 9, 11, 19, 20, 5, 6, 7 hours) than at night. The longest inversion of the circadian rhythm GPVR in the acute period of SCTBI was found in group 3. Hyperdynamic orientation of the adaptive restructuring of blood circulation was revealed in groups 1 and 3 of injured children older than 7 years.*

Keywords: *circadian rhythm, total peripheral vascular resistance, severe concomitant traumatic brain injury, children older than 7 years.*

Relevance. Concomitant traumatic brain injury (CTBI) accounts for 43-68% in the structure of concomitant injuries and is observed in 23-63% of patients with severe traumatic brain injury (TBI). Postoperative mortality in patients with CTBI is 46.8% according to the authors. More than half of patients with severe TBI typically have multiple lesions that result in significant blood loss, systemic hypotension, and hypoxia. Prevention or justified intensive therapy of these secondary pathological processes allows, in most cases, to significantly improve the outcomes of TBI. The hyperkinetic type of blood circulation may also be due to a sharp increase in the concentration of adrenaline in the blood. Violation of oxygen delivery to the brain, with an increase in its oxygen demand, leads to the fact that the brain becomes more susceptible to additional damaging factors,

such as fluctuations in blood pressure, hypoxia, and violation of the rheological properties of blood. These secondary damaging factors complicate the condition of patients with TBI in more than 50% of cases. The norm of general peripheral vascular resistance (GPVR) is considered when its value fluctuates within 1000 dyn.s.cm^{-5} [1-4]. Due to the lack of information on hemodynamic features in severe concomitant traumatic brain injury in school-age children (7.1-18 years old), we tried to study the change in the structure of the phase characteristic in the acute period and assess the response of the GPVR circadian rhythm to severe concomitant traumatic brain injury. trauma.

Objective. To study and identify the features of the circadian rhythm of the total peripheral vascular resistance in children with severe concomitant traumatic brain injury at school age.

Material and research methods. The indicators of a comprehensive examination of 36 patients of school age (7-18 years old) with severe concomitant traumatic brain injuries (SCTBI), admitted to the intensive care unit (ICU) of the neurosurgical department of the Republican Scientific Center for Emergency Medical Aid (RSCEMA) in the first hours after a traffic accident (RTA) - 33, catatrauma - 3 patients. All patients admitted to the RRCEM were operated on in the first hours after the injury, in extremely severe cases, with simultaneous resuscitation and correction of serious violations of vital organs and systems at the same time.

Continuous hourly monitoring of hemodynamic parameters, including SBP, was performed for 30 days after CSTBI. According to the indications, patients were started on invasive mechanical respiratory support (MRP) at admission. Mechanical respiratory support was started on artificial lung ventilation (CMV) for a long time, with subsequent transfer to SIMV. Restoration of adequate spontaneous breathing and reflexes was an indication for extubation. The assessment of the severity of the condition was carried out by the methods of scoring on the scales for assessing the severity of concomitant injuries - the PTS scale (PediatricTraumaScore (PTS) (Tepas J.J. et al. 1985), assessment of the severity of injuries on the ISS scale, the severity of acute cerebral insufficiency on the Glasgow coma scale. On admission, impairment of consciousness in 14 injured patients was assessed on the Glasgow Coma Scale (GS) as 8 points or lower. Patients were considered in three groups according to the duration of intensive care in the ICU. Group 1 with the duration of intensive therapy (7.1±1.8 days) included 11 children aged 11.5±2.4 years, 2 - duration of stay in the ICU 13.9±1.9 days consisted of 9 patients, mean age 12.5±2.5 years, 3 - 16 patients aged 11.2±2.3 years with a duration of treatment in the ICU from 21 to 30 days. Comprehensive intensive care included the identification and timely correction of deviations: mechanical respiratory support (MRP), analgesic, anti-inflammatory, hemostatic, antibacterial, infusion therapy, compensation for

CBV deficiency, correction of protein, water and electrolyte balance disorders, after surgical removal from shock to the extent of permissible possibilities of early correction, stress-limiting, cytoprotective therapy.

Results and discussion.

On day 1, the mesor of the circadian rhythm GPVR in groups 1 and 3 did not differ from the normative limit, while in group 2 there was an increase of 60% ($p<0.05$) than in group 1. In dynamics, patients of group 1 showed a significant increase in the mesor of the circadian rhythm GPVR on day 4 by 36%, by 5–35%, on day 6–26%, and by 33% on day 7 ($p<0.05$, respectively). Thus, in group 1, the systemic inflammatory response to injury was manifested by an increase in GPVR on days 4–7 in the acute period of SCTBI. While in patients of the 2nd group, GPVR increased by almost 50% on day 1 in the following days showed a tendency to decrease, significantly decreasing by 34% only on the 15th day ($p<0.05$) (table 1).

Table 1.

Mesor dynamics of the circadian rhythm GPVR (dyn.s.cm¯5)

Days	Group 1	Group 2	Group 3
1	946±114	1514±325*	1149±138
2	1065±69	1163±105	1197±28
3	1157±65	1262±52	1244±86
4	1286±73●	1176±72	1414±111
5	1267±61●	1271±63	1513±64
6	1197±69●	1392±80	1504±68
7	1259±107●	1273±87	1460±77
8	1093±57	1198±101	1373±98
9	1084±73	1514±149	1351±58
10		1148±72	1397±109
11		1207±166	1406±86
12		1230±101	1496±105
13		1356±62	1290±90
14		1353±128	1540±96
15		988±108●	1390±87
16			1397±80
17			1374±61
18			1500±92
19			1458±67
20			1477±92
21			1344±67
22			1388±84
23			1346±69

24			1427±113
25			1715±124
26			1617±113
27			1812±187
28			1755±151
29			1672±203
30			1456±164

‴-significant relative to the indicator in group 1

Table 2.

GPVR hourly dynamics (dyn.s.cm ¯5)

Days	Group 1	Group 2	Group 3
8	1142±81	1311±181	1464±125‴
9	1163±65	1282±165	1442±158‴
10	1107±108	1319±177	1394±133
11	1079±121	1271±172	1463±165‴
12	1144±141	1254±186	1452±146
13	1208±100	1266±164	1422±174
14	1141±151	1279±158	1425±136
15	1112±136	1280±172	1393±148
16	1103±120	1284±184	1409±129
17	1130±123	1244±123	1422±157
18	1124±141	1282±127	1406±137
19	1140±79	1258±133	1449±146‴
20	1183±78	1255±127	1441±177‴
21	1211±113	1293±181	1464±149
22	1184±82	1247±122	1444±159
23	1172±130	1256±101	1433±155
24	1202±110	1239±104	1425±139
1	1221±148	1211±120	1492±180
2	1189±113	1269±112	1431±125
3	1148±101	1296±153	1497±172
4	1140±105	1281±153	1514±194
5	1151±95	1250±130	1505±149‴
6	1138±86	1263±139	1498±158‴
7	1101±98	1281±204	1494±123‴

*-significant relative to the indicator in group 1

●-significant relative to the indicator in 1 day

As shown in tab. 2, a significantly significant difference was found between the average hourly GPVR indicators for the entire acute period between the parameters in groups 1 and 3, when the GPVR values in children of group 3 were higher than in group 1 in 8, 9, 11, 19, 20, 5, 6, 7 hours by 28%, 24%, 35%, 27%, 21%, 31%, 31%, 35% ($p<0.05$, respectively).

A direct effect of the severity of SCTBI on the average GPVR in the acute period of traumatic illness was found (fig. 1).

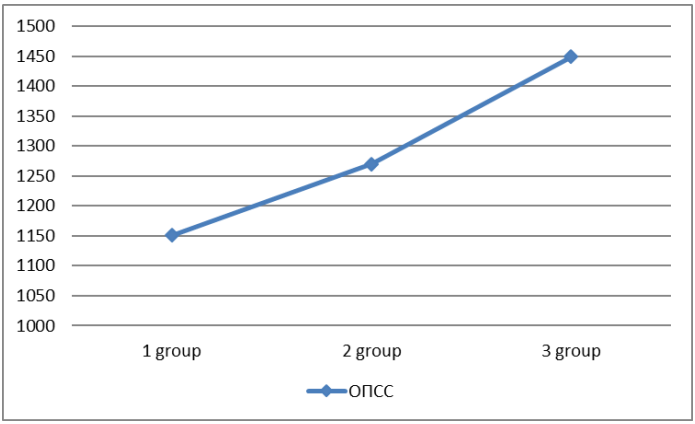

Figure 1. *Dynamics of GPVR depending on the severity of injury in children older than 7 years, (dyn.s.cm¯5).*

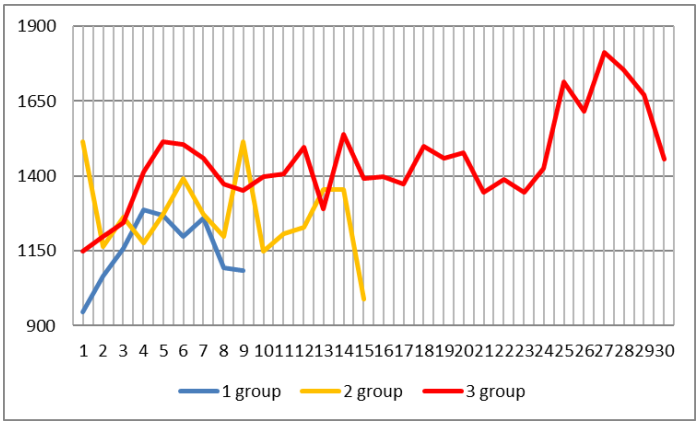

Figure 2. *Dynamics of the mesor of the circadian rhythm GPVR older than 7 years, (dyn.s.cm¯5).*

During the acute period of SCTBI, undulating fluctuations in the mesor of the circadian rhythm GPVR were detected in group 1 with an increase in the period of about a week to 9 days, in group 2, a shortening of the period of fluctuations to 6, 5.4 days. In group 3, the instability of the wavelength of the circa-weekly rhythm was noted, amounting to 8,5,4,5,4,4 days (fig. 2). The revealed deformation of the structure of the around-week biorhythm is due not only to the stress reaction, but also to the effect of complex intensive care on GPVR. Attention was drawn to the difference in hourly monitoring of the GPVR indicator (fig. 3). Thus, the average level of daily fluctuations in GPVR in group 1 did not exceed 1200 dyn.s.cm^{-}5, in group 2 - 1300 dyn.s.cm^{-}5. And the most significant increase in GPVR, regardless of the time of day, was in group 3, amounting to 1400-1500 dyn.s.cm^{-}5.

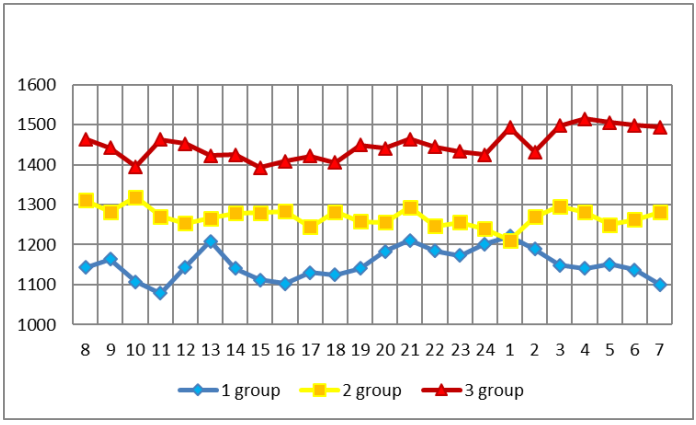

Figure 3. *Hourly monitoring of GPVR in the acute period of SCTBI over 7 years, (dyn.s.cm^{-}5).*

The amplitude of the GPVR circadian rhythm was also oscillatory. Moreover, the smallest value of the amplitude of daily fluctuations in GPVR was found in group 1, slightly higher in group 3, and the largest amplitude with a maximum increase on days 1 and 8 up to 1900 dyn.s.cm^{-}5 was found in group 2 of children (fig. 4). We understood what was revealed as an adaptive response to trauma under conditions of less stress-protective therapy.

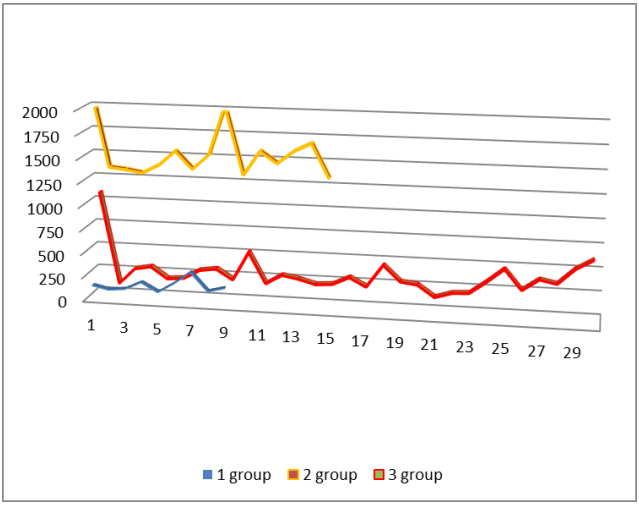

Figure 4. *Dynamics of the amplitude of the circadian rhythm GPVR, (dyn.s.cm¯5).*

The longest inversion of the GPVR circadian rhythm was found in group 3 (fig. 5), which confirmed the correspondence between the severity of shifts in the peak of the acrophase and the severity of the condition of the injured children. Significantly significant inverse correlation between GPVR and CO was found in 1 (-0.87) and 3 (-0.9) groups of children.

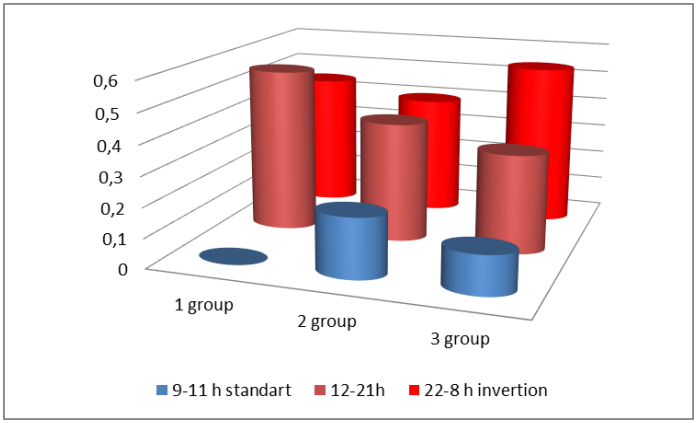

Figure 5. *Duration of acrophase peak shift in the acute period of SCTP older than 7 years, %.*

The hyperdynamic nature of the adaptive restructuring of blood circulation also corresponded to feedback in groups 1 (-0.83) and 3 (-0.73) (tab. 3). While in group 2, the correlation of hemodynamic parameters was insignificant. It gives the impression of a relatively more pronounced adaptive reaction of the peripheral vascular system under conditions of stress-protective intensive care for injured children of the 2nd group (fig. 6).

Table 3.

	Group 1	Group 2	Group 3
GPVR/CO	-0,87	-0,68	-0,90
GPVR/SV	-0,83	0,14	-0,73
GPVR/MBP	0,43	-0,04	0,00
GPVR/PBP	-0,45	-0,12	-0,55
GPVR/DBP	0,75	-0,21	0,49
GPVR/T°	0,39	-0,04	-0,03
GPVR/SBP	0,17	-0,17	-0,19

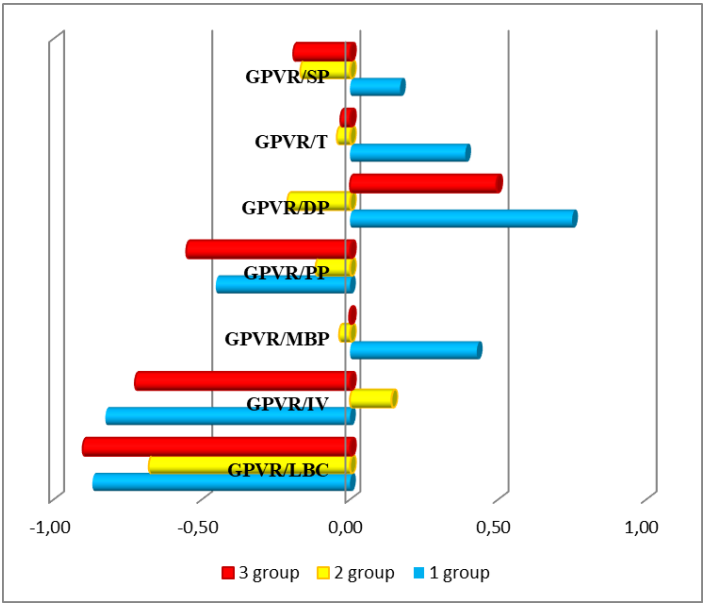

Figure 6. *GPVR correlations older than 7 years*

Conclusion. On day 1, the mesor of the circadian rhythm GPVR in groups 1 and 3 did not differ from the normative limits, while in group 2 an increase of 60% was noted. It was revealed that the GPVR values in children of the 3rd group were higher than in the 1st and 2nd groups to a greater extent during the day (at 8, 9, 11, 19, 20, 5, 6, 7 hours) than at night. The longest GPVR circadian rhythm inversion was found in group 3. Hyperdynamic orientation of the adaptive restructuring of blood circulation was revealed in groups 1 and 3 of injured children older than 7 years.

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FEATURES OF REACTIVE EDEMA OF THE EYELIDS IN ENT PATHOLOGY

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Abstract. *The article presents the result of a retrospective non-randomized study of children with reactive eyelid edema treated in a pediatric ENT department. Clinical features of the course of the disease were revealed: boys get sick more often (55%), in the autumn season (28.3% of patients), the average age of children is 4.6 years, with a length of stay in the hospital - 7.8 days. Peripheral blood leukocyte indices were calculated: leukocyte shift, marker of viral infections, allergization index, which can be used as diagnostic criteria for management of this category of patients.*

Keywords: *reactive eyelid edema, rhinosinusogenic orbital complications, leukocyte indices*

Relevance. Rhinosinusogenic orbital complications are quite common at present, despite the high level of medical care and high-tech diagnostic methods. Such severe complications as phlegmon of the orbit or thrombosis of the veins of the orbital fiber, cavernous sinus are much less common, and cases of their occurrence are associated with a lack of timely seeking medical help or insufficient treatment [1]. In recent years, only isolated cases of loss of vision as a result of the development of orbital phlegmon have been found in the literature. The frequency of serious complications is quite low (from 6.25% to 78% according to different lit-

erature sources), however, such complications are associated with significant morbidity, disability and high mortality [2,3]. In the pre-antibiotic era, orbital cellulitis resulted in death from meningitis in 17% of cases and blindness in 20%. However, in the era of antibiotics, the incidence of meningitis is 1.9% in patients with orbital cellulitis despite prompt treatment with systemic antibiotics and surgery [2,4]. The prevalence of rhinosinusogenic orbital and intracranial complications, according to the pediatric ENT department, is high, does not tend to decrease, and accounts for 12% of all purulent-inflammatory diseases of the nose and SNPs [5]. Most often, the infection develops as a result of polysinusitis, occurs on the face or eyelids after a recent injury, odontogenic abscess, or by hematogenous spread from a distant source [6]. According to literature sources in children, in almost all cases, orbital phlegmon was preceded by sinusitis with multiple lesions of the sinuses, these results in our country correspond to the results of Western countries [7,8]. In a smaller percentage of cases, but cases of dacryocystitis, dental infection, endophthalmitis, ethmoidal sinusitis have been reported as causes of orbital phlegmon [8]. The most common localization of sinusitis was inflammation of the ethmoid and maxillary sinuses. In children, several sinuses are predominantly involved, while in adults only one sinus is usually involved [9,10]. With untimely or incorrect diagnosis and treatment during the spread of infection, preseptal complications can progress, turning into postseptal ones, and in especially severe cases, lead to optic neuritis or intracranial complications, such as cavernous sinus thrombosis, brain abscess, meningitis [11,12, 13]. Therefore, the occurrence of orbital complications remains an urgent problem, despite the constant improvement of treatment and diagnostic methods, and requires the joint work of ophthalmologists, otorhinolaryngologists and pediatricians [13,14].

Purpose of the study. To identify the features of the course of reactive eyelid edema in patients of the otorhinolaryngological department of the children's hospital SBHCI TO "Oblast Clinical Hospital No. 2" for 2017-2019 with the calculation of peripheral blood indices.

Materials and methods. A retrospective non-randomized study of 120 discharge reports of patients who received medical care in the pediatric otorhinolaryngology department of SBHCI TO "Oblast Clinical Hospital No. 2" in 2017-2019 with a diagnosis of rhinogenic orbital complications: reactive eyelid edema was carried out. Upon admission and during the entire period of treatment, patients were examined using physical, laboratory and instrumental research methods. All patients underwent: complete blood count (CBC), radiography of the paranasal sinuses (PS), computed tomography (CT) of the paranasal sinuses (PN). Peripheral blood indices were chosen as a marker for determining the activity of the inflammatory process and impaired immunological reactivity: leukocyte index (LCI), allergization index (AI), viral infection marker (VIM) [15,16]. The formula for calculating

the LCI indicator: (eosinophils + basophils + myelocytes + metamyelocytes + stab + segmented) / (monocytes + lymphocytes). The reference LCI value is 1.96 ± 0.56. The formula for calculating AI = (lymphocytes % + 10 x (eosinophils % + 1)) / (neutrophils % + monocytes % + basophils %). Reference value AI 0.68-1.08. The formula for calculating the VIM indicator = (lymphocytes %) / (monocytes %). The reference value of VIM is 5.34+0.59. Statistical analysis of the results obtained was carried out using statistical packages STATISTICA (version 10, license agreement № 4190051 of 03.05.2019).

Results and discussions. According to our study, among patients hospitalized with rhinogenic orbital complications, manifested by reactive eyelid edema, boys predominated - 55% (66 people), girls accounted for 45% (54 people). Median age of patients with reactive eyelid edema is 4.6 years, interquartile range (Q_1; Q_3) 1 month - 18 years. In the vast majority (40.8%), children under 3 years of age were treated. The proportion of hospitalized children aged 3 to 4 years was 26.7%, from 5 to 7 years - 9.2%, from 8 to 12 years -12.5%, from 13 to 15 years - 7.5%, from 16 to 18 years old - 3.3%. The average length of stay of children in the hospital was 7.8 days. The duration of the main disease of patients before hospitalization was on average 9 days, while the occurrence of ophthalmic manifestations was observed on average only 2.4 days before going to the emergency department. From this we can conclude that reactive eyelid edema appeared on average 6.6 days later than the symptoms of the underlying disease. In the study of the predominant time for the appearance of reactive eyelid edema during the year, seasonality was revealed, the peak incidence occurs in the autumn season (fig. 1).

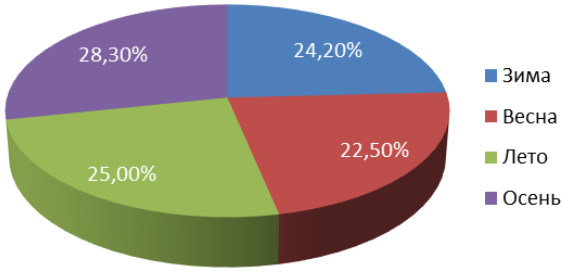

Figure 1. *The structure of reactive eyelid edema depending on the season*

In the process of studying the data of admission to the department with rhinogenic orbital complications for individual months, it was found that the majority of hospitalized children went to the emergency department in February, July and September - 12 people each (10% each). In turn, in March, June, October and

November, 11 people each (9.2% each) applied for medical help with edema, and 9 people each (7.5% each) in April and December. Even less often, treatment with reactive edema of the eyelids occurred in January - 8 people (6.6%), as well as in May and August - 7 people each (5.8% each).

In the study group of patients with rhinogenic orbital complications, peripheral blood indices were calculated, while the LCI was 2.37 + 0.3; AI - 1.13+0.10; VIM - 3.61+0.21 at ($p<0.05$). Thus, it can be assumed that with an LCI of 2.67+0.3 or less, AI <1.23; VIM<3.82 patients with rhinogenic orbital complications develop reactive edema.

Conclusions

1. According to the results of our study, the seasonality of the occurrence of reactive eyelid edema in children was revealed: they occurred in the autumn season (28.3% of patients), mainly in September (12 patients).

2. Boys were sick more often (55% of patients), the average age of children was 4.6 years, the stay of children in the hospital was 7.8 days.

3. The obtained results of peripheral blood indices (LCI, VIM, AI) can be used as diagnostic criteria for the choice of tactics for the treatment of rhinosinusogenic complications of the orbit.

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FIBROBLAST AS THE MOST IMPORTANT CELL OF THE INFORMATION CELLULAR MICROENVIRONMENT: ANALYSIS OF FIBROBLAST DENSITY IN NON-TUMOR PATHOLOGY OF THE CERVIX AGAINST THE BACKGROUND OF CONNECTIVE TISSUE DYSPLASIA

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Abstract. The components of stroma *(extracellular matrix (ECM), various connective tissue cells) play a leading role in epithelio-stromal relationships, the nature of which changes in dysplasia of connective tissue (DCT), reflected in numerous stigmas of dysmorphogenesis and the course of various types of pathology. Fibroblasts are among the most important cells of the stroma; they are responsible for self-renewal and remodeling of the ECM and have a powerful morphogenetic effect on tissues. In order to identify the features of the state of the subepithelial stroma, an analysis of clinical data and a morphological study (light microscopy and morphometry) of cervical biopsy specimens in background and precancerous processes in the presence (group 1) and absence (group 2) of concomitant DCT was carried out. The results of the study showed that statistically significant differences in the density of fibroblasts (by groups, respectively, Me=36.4; Q25=25.8; Q75=45.0 and Me=18.0; Q25=15.0; Q75=21.8; p=0.05) and relative surface area of vessels (by groups Me=8.0; Q25=4.5; Q75=10.1 and Me=3.1; Q25=1.7; Q75=4.9; p<0.05) in the presence of DCT (group 1) were associated with a high incidence of epithelial dysplasia (CIN) in this group (72.9%, in group 2 - 16.4%, p=0.0000), in the second group the frequency of leukoplakia prevailed (41.8%, in group 1 - 16.2%, p=0.0000). The noted features were combined with multidirectional changes in the hormonal status - a high incidence*

of hormonal disorders such as hypothyroidism (28.3%) and hyperprolactinemia (39.2%) in the group with CTD and the prevalence of hyperestrogenemia (36.3%) and hyperandrogenemia (30.9%). %) in the second group (in all cases $p<0.05$). It cannot be ruled out that the presence of DST determines a different nature of epigenomic influences and determines the features of the course of pathology against its background.

Keywords: *background and pre-tumor processes in the cervix uteri; systemic non-differentiated dysplasia of connective tissue; density of fibroblast; hormonal status.*

Introduction

According to modern concepts, field cancerization in epithelia (and this is the skin and mucous membranes of various organ localization) is characterized by the coevolution of the stromal and epithelial compartments along the path of accumulation of genetic, epigenetic disorders in their cells and changes in the immune status of the tissue with a gradual change in the cellular phenotype of the epithelium from normal to precancerous (metaplasia, leukoplakia, dysplasia) and tumor, when cells acquire the ability for epithelial-mesenchymal transition, invasion and metastasis [1, 2, 3, 4]. At the same time, changes in the tissue stromal compartment, or ECM and connective tissue cells, can play a leading role in the initiation of the tumor process, which is determined by the appearance of a specific tumor-associated phenotype of fibroblasts, macrophages, various immune cells and changes in their functional characteristics [1, 5].

The components of the stroma, represented by extracellular matrix (ECM) and various cellular elements of the connective tissue (fibroblasts, microvascular endothelium, pericytes, macrophages, lymphocytes, and others), play a leading role in epithelio-stromal relations, form the microenvironment of epithelial cells and are responsible for the most important processes in their life (proliferation, formation of cell polarity, differentiation, migration and apoptosis), having a direct influence and through modeling the effects of various signaling molecules - cytokines, growth factors, hormones, etc.

Among stromal cells, the most important role belongs to fibroblasts, which are responsible for self-renewal and remodeling of ECM, preservation of stem cell niches, and tissue homeostasis in general.

Fibroblasts have a powerful morphogenetic effect on tissues due to a wide range of intercellular interactions (regulation of inflammatory and immune processes) and the synthesis of a large number of biologically active substances - various CK and chemokines (IL-1; IL-6; TNFα), growth factors (TGFβ; EGF), including angiogenic factors (VEGFs, FGFs, HGF/SF, angiopoietin-1), as well as hormones and neuropeptides identical to those in the central nervous and endocrine systems.

Fibroblasts themselves exhibit pronounced phenotypic plasticity, transforming in the focus of chronic inflammation or tumor growth under the influence of various stimuli (TGF, EGF, PDGF, FGF2) into myofibroblasts (MFBs).

With dysplasia of connective tissue (DCT), associated with genetically determined, congenital or acquired structural anomalies (defects in structural connective tissue proteins, enzymes for the synthesis and breakdown of ECM, numerous growth factors, their receptors and antagonists), the nature of epithelio-stromal relationships changes, which finds reflection not only in various stigmas of dysmorphogenesis, but also in the course of various types of pathology against the background of DCT, including obstetric and gynecological diseases.

The reorganization of the ECM in the tissues of the female genital tract, or the so-called cervical remodeling, is of great importance both in the process of performing the reproductive function and in pathology - the development of fibrosis and carcinogenesis.

Aim of the work is to identify the features of the state of the subepithelial stroma in background and precancerous processes in the cervix associated with systemic undifferentiated connective tissue dysplasia.

Materials and methods

A comparative analysis of the results of a clinical examination (examination, colposcopy, microbial flora by PCR, a study of the level of sex hormones, thyroid hormones, corresponding pituitary tropic hormones) and a study of biopsy material of 129 women aged 22 to 51 years with background and precancerous processes in the cervix, of which 74 patients, who also had visceral signs of systemic undifferentiated DCT, made up the 1st group; 55 patients without signs of DCT - group 2. The groups were comparable in terms of the age of the patients (the mean age in the groups was 39.±4.6 and 37.7±5.1 years, respectively), the incidence of cervical ectopia (in groups, 74.3 and 67.3%), sexual infections (47.3 and 63.6%), including infection with oncogenic strains of HPV - human papillomavirus (60.8 and 60.0%). In all cases, voluntary informed consent of patients was obtained for the use of the results of their examination in the work, and permission was also received from the ethical committee of Surgut State University (protocol № 15, 05/15/2019).

According to the principle of group formation, the study is retrospective. The criteria for inclusion in the study were clinical and morphological verification of background and precancerous changes in the cervix, for group 1 - also the presence of external and/or visceral signs of DCT in patients (involvement of three or more organs of different systems in the process), documented by data instrumental research methods (fibrogastroscopy, ultrasound examination of internal organs, echocardiography, computed tomography, etc.) and the results of examination of patients by various specialists (in particular, the frequency of stigmatization of the

genitourinary system was 68.9%), for the second - on the contrary, their absence. The criterion for exclusion from the study for both groups was the presence of signs of active inflammation in cervical biopsy specimens (pronounced inflammatory cell infiltration, edema, etc.).

Light microscopy and morphometry of paraffin sections of cervical biopsy specimens 3–4 μm thick, stained with hematoxylin and eosin were carried out using a Nikon Eclipse Ni M570E microscope (Japan) and NIS-Elements BR computer software after obtaining a digital image with the help of - Nikon DS-Fi2 video cameras (Japan). In the course of a morphometric study, all cells of the subepithelial stroma corresponding to the FB phenotype (MFB) at the light-optical level were counted using a morphometric grid with a square area of 10,000 micron^2 at a magnification of 200. The relative surface area of the vessels was calculated as a fraction of the total area of the transverse sections of vessels from the total area of the stromal compartment of the slice in each case in all fields of view.

Statistical processing of the obtained data was carried out using the Microsoft Excel 2010 and Statistic 10.0 software package. After checking the type of distribution of the data obtained by the Shapiro-Wilk method, to assess the differences in the compared indicators (morphometry data) in the studied groups, the nonparametric Mann-Whitney test was used to determine the median (Me), first (Q1) and third (Q3) quartiles. For a comparative analysis of qualitative indicators (the frequency of detected hormonal disorders) presented as a percentage (%) of the total number of observations in each group, the Yates-corrected $\chi 2$ test and Fisher's exact test (F) were used. The critical level of significance in testing statistical hypotheses was taken equal to 0.05.

Results and its discussion

With comparability of groups in terms of the frequency of infection with oncogenic strains of HPV in cervical biopsies in the group with DCT (group 1), tendencies to hyperplasia of the glands and glandular epithelium with the appearance of its pseudo-multi-row and often papillary growths prevailed; to the formation of cysts with an epithelial lining of a different phenotype - from prismatic to flattened epithelium; the appearance of foci of acanthosis. In biopsy specimens of the 1st group, cervical intraepithelial neoplasia (CIN) of I-III degree was also more often detected (72.9%, in group 2 - 16.4%, p=0.0000), in one case, invasive squamous cell carcinoma of the cervix was diagnosed. In biopsy specimens of the group 2, moderate hyperplastic changes in the integumentary epithelium, rare glands, and also the predominance of the frequency of leukoplakia (41.8%, in the 1st - 16.2%, p=0.0000).

The high frequency of CIN in the 1st group was associated with a higher density of fibroblasts (the number of cells per 10,000 μm2) of the subepithelial stroma (by groups, respectively, Me=36.4; Q25=25.8; Q75=45.0 and Me= 18.0; Q25=15.0;

Q75=21.8, p=0.05) and the relative surface area of the vessels (by groups, respectively Me=8.0; Q25=4.5; Q75=10.1 and Me=3.1; Q25=1.7; Q75=4.9, p<0.05). The subepithelial stroma was more often characterized by a pronounced density of collagen fibers, in some cases, foci of hyalinosis and a high density of fibroblasts, among which two phenotypes were clearly differentiated - narrow spindle-shaped cells sandwiched between the fibers of the connective tissue with a dark cytoplasm and a hyperchromic nucleus and more large spindle-shaped cells with a relatively light cytoplasm and a nucleus with a well-defined nucleolus, located in a looser stroma.

Smaller dark fibroblasts are described as immature fibroblasts, or fibrocytes, transformed under the influence of various growth factors into MFBs, characterized by high functional activity with the production of a large amount of fibronectin and various collagen isoforms [6], as well as the presence of receptors for various hormones and the ability to synthesize hormones (in particular, thyroglobulin) [7, 8]. Such a phenotype is also characteristic of tumor-associated fibroblasts (CAFs), which appear in tissue even before tumor transformation of epithelial cells [5]. It is noted that the content of more than 50% of immature fibroblasts in tissues correlates with increased vascular density, the appearance of tumor-associated macrophages, and the epithelial-mesenchymal transition [5].

An important consequence of the high FB density may be the accumulation of fibroblast growth factor (FGFs) in the tissue, which is not only a powerful angiogenic factor, but also, regardless of the presence of the corresponding ligands, can lead to the activation of steroid receptors (in particular, replace estrogens by acting on ER - estrogen receptors) and their associated signaling cellular pathways leading to an increase in cell proliferative activity. Thus, FGFs are considered as the most powerful mediator of tumor transformation in breast cancer [9].

The noted features of the exocervix response were combined with multidirectional changes in the hormonal status in the studied groups - a significant frequency in patients of the 1st group of hypothyroidism (29.7%, in the second group - 12.7%, p = 0.0220) and hyperprolactinemia (37.8%, in the second group - 3.6%, p=0.0000), in women of the 2nd group - hyperestrogenemia (36.4%, in the first - 1.4%, p=0.0000) and hyperandrogenemia (23.6%, in the first - 4.1, p=0.0010).

Conclusion

Thus, in the background and precancerous processes in the cervix associated with systemic undifferentiated DCT, in comparison with the same pathology in the absence of DCT, there was a statistically significantly higher density of fibroblasts in the exocervix stroma in combination with a high relative surface area of the vessels and a higher frequency of CIN I-III degree, as well as a different nature of hormonal disorders (hypothyroidism, hyperprolactinemia), which theoretically can lead to various effects, in particular the formation of a “tumor field”. Accord-

ing to modern concepts, the formation of a "tumor field" is associated with background and precancerous changes in tissues, which manifest themselves in such phenomena as hyperplasia, dysplasia, angiogenesis, and violations of epithelial-stromal relationships.

It cannot be ruled out that DST with its characteristic disturbances in the ECM, hormonal and immune homeostasis is an important factor in the epigenomic influence that determines the characteristics of the course of pathology against its background.

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THE STUDY OF THE NUMBER OF VISITS IN PATIENTS DURING THE PERIOD OF ADAPTATION TO REMOVABLE LAMELLAR DENTURES AGAINST THE BACKGROUND OF THE USE OF A PROBIOTIC AND SYNBIOTIC IN A COMPARATIVE ASPECT

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Abstract. *The influence of removable dentures on the tissues and organs of the dental system is diverse, as well as the body's responses. Various pathogenic mechanisms underlie the development of prosthetic field tissue reactions. The microflora of the oral cavity is a highly sensitive indicator system that reacts with quantitative and qualitative shifts to changes in the state of various organs and systems of the human body. Under the influence of various factors, including removable dentures, the composition of the microflora can change, which can lead to the development of oral dysbiosis, which worsens the results of orthopedic treatment. To prevent oral dysbiosis in orthopedic treatment of patients with removable lamellar dentures, it is possible to use biotherapeutic methods that involve the use of local and systemic action of synbiotics, probiotics.*

Keywords: *removable dentures, acrylic polymers, probiotic, synbiotic.*

The relevance of research

The development of reactions of tissues of the prosthetic field is based on various pathogenetic mechanisms due to the properties of the materials from which

the prosthesis is made, the methods of its fixation, the nature of the transmission of masticatory pressure, and the value of the basis of the prosthesis. The responses of the prosthetic bed are determined, on the one hand, by the nature, intensity and duration of the stimulus, and on the other hand, by the reactivity of the organism. Great importance in modern dentistry is given to the study of normal human microflora, since its participation in the processes of digestion, metabolism, vitamin synthesis, the formation of the immune status and the general nonspecific resistance of the body has been proven. The course, outcome and prognosis of orthopedic treatment depend on microecological well-being. Microbiocenosis of the oral cavity, both in normal and pathological conditions, is represented not only by bacteria, but also by viruses, fungi, yeasts, spore forms of microorganisms, etc., which, like in other parts of the body, are in complex ecological relationships. It has been established that in patients with dysbiotic changes, the hygienic condition of the oral cavity and, accordingly, of removable dentures worsens. This, in turn, dictates the need to develop and introduce into dental practice means and methods that normalize the biocenosis. In recent years, there has been an active development of modern drugs - synbiotics, which include a complex of probiotics and prebiotics. Stimulation of probiotics by prebiotics contributes to the regulation of metabolic activity, the development of beneficial microbiota, the inhibition of potential pathogens, and the provision of immunomodulatory effects. However, the effect of the above drugs on the oral mucosa, oral microflora and hygiene of removable dentures in patients with removable orthopedic structures remains not fully understood.

Thus, the search and development of new complex methods for the prevention of oral dysbiosis that occurs when using removable dentures remains one of the topical issues of modern dentistry, due to the widespread prevalence of this problem. However, at present, the effectiveness and feasibility of including these drugs in the prevention of oral dysbiosis in patients with removable dentures are few and insufficiently studied, as well as studies conducted to increase the degree of patient adherence to doctor's recommendations.

Materials and research methods.

To solve the tasks set in the clinic of orthopedic dentistry, orthopedic treatment was examined and carried out for the complete and partial absence of teeth in the upper and lower jaws of 60 patients without severe chronic diseases of the oral mucosa and severe somatic pathology. The general characteristics of the studied patients are presented in table 1.

Table 1

Analysis of patients with removable lamellar dentures made of acrylic polymers who took part in the study

Features	Number of subjects	%
Number of patients	60	100
Male patients	27	45
Female patients	33	55
Age of study patients		
45 – 49 years	12	20
50 – 59 years	16	26,7
60 – 69 years	26	43,3
70 – 80 years	6	10
The state of the dentition in the studied patients		
Partial absence of teeth in both jaws	16	26,7
Partial absence of teeth in the upper jaw	10	16,7
Partial absence of teeth in the lower jaw	14	23,3
Complete absence of teeth	5	8,3
Complete absence of teeth in the upper jaw; partial absence of teeth in the lower jaw	9	15
Complete absence of teeth in the lower jaw; partial absence of teeth in the upper jaw	6	10

For the study, subjects were selected without concomitant allergic and autoimmune diseases, recurrent herpetic, cytomegalovirus and chlamydial infections. Also, some patients had a history of general diseases, but only chronic, in remission.

Patients had varying degrees of anatomical-topographic and anatomical-physiological features of the prosthetic bed, which are of direct importance for treatment in the clinic of orthopedic dentistry. Based on this, 3 groups were formed:

- I the group consisted of 20 patients who were made removable lamellar dentures made of acrylic polymer “Ftorax”;

- II the group consisted of 20 patients who were made removable laminar dentures made of acrylic polymer “Belacryl-E GO”;

- III the group consisted of 20 subjects who were made removable dentures from the acrylic polymer “Belacryl-E GO”; they were prescribed applications on the mucous membrane of the oral cavity of the “Asepta with propolis” gel modified with the probiotic “Bifiliz” daily for 10-15 minutes, for 30 days; synbiotic “Bifistim” 1 tablet per day for resorption, for 30 days; conducted a conversation with the subjects in order to increase compliance with treatment and oral hygiene.

Clinical methods of examination were carried out in accordance with the

"Protocol for the management of patients with partial absence of teeth (partial secondary adentia)". Patients were asked to take an anamnesis, fill out a medical record, and conduct a questionnaire.

Research results

In the course of clinical observations of patients after fixation of removable lamellar dentures, the number of visits to patients of each of the studied groups for corrections during the period of adaptation to them was studied. The total number of visits to patients for corrections in group 1 (base of acrylic plastic "Ftorax") was 46, in group 2 (base of acrylic polymer "Belacryl-E GO") - 34, in group 3 (base of polymer "Belacryl-E GO") - 12. Thus, the average number of visits was: in group 1 - 2.3; in group 2 - 1.7; in group 3 - 0.6. Analysis of the results of the study is presented in table 2.

Table 2

The number of visits to patients for the correction of prostheses

Groups of patients, material of bases for removable dentures	Number of studied patients	Number of visits to study patients for prosthesis correction	Average number of visits for denture correction
1 – acrylic polymer «Ftorax»	20	46	2,3
2 – acrylic polymer «Belacryl-E GO»	20	34	1,7
3 – acrylic polymer «Belacryl-E GO», complex technique	20	12	0,6

It was found that when using prostheses with a base layer of acrylic polymer "Ftorax", the average rate of visits for corrections was the maximum. The use of plate prostheses with bases made of acrylic plastic "Belacryl-E GO" made it possible to reduce this indicator by 1.3 times. However, a significant decrease in the number of visits for corrections in the adaptation period was noted in patients who used removable lamellar dentures with bases made of acrylic polymer "Belacryl-E GO" while taking a synbiotic and a gel for treating the oral mucosa modified with a probiotic (fig. 1).

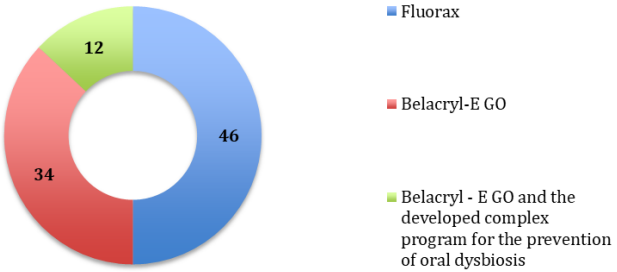

Figure 1. *Analysis of the number of visits to patients for the correction of removable dentures*

Conclusions:

The use of acrylic plastic "Belacryl-E GO" and the developed complex method for the prevention of oral dysbiosis, which consists in taking a synbiotic and a gel for treating the oral mucosa, modified with a probiotic allowed to reduce the inflammatory reaction of the mucous membrane of the prosthetic bed and increase its resistance to the negative effects of a removable denture during the period of adaptation. In turn, this led to a decrease in the number of visits for the purpose of correcting a removable prosthesis, as well as a reduction in the period of adaptation, which made it possible to improve the quality of life of patients with complete or partial absence of teeth, not only at the initial stage of adaptation, but also during the entire period of using a removable lamellar denture.

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OBSTETRIC AND PERINATAL OUTCOMES OF PRETERM LABOR WITH A LONG WATERLESS INTERVAL

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Summary. *The results of a comparative study of the features of the course and outcomes of preterm labor (PL) complicated by premature rupture of the fetal membranes (PRFM) with an waterless interval of more than 12 hours (group 1: n=153) and spontaneous PL with an waterless interval of less than 12 hours (group 2: n= 408) are presented. It was revealed that pregnancy in group 1 was significantly more frequent against the background of acute respiratory diseases (ARVI – 2 times), colpitis (2.6 times), threat of pregnancy termination (1.3 times), isthmic-cervical insufficiency (1.3 times), increasing the likelihood of chorioamnionitis in labor (5.7 times). It was found that in the 1st group of patients, the risk of developing hyperthermia in the postpartum period significantly increased (by 2 times - up to 49.7%), uterine subinvolution (by 1.5 times – up to 25.5%), late hypotonic bleeding (by 13 times – up to 6.5%), endometritis (by 4 times – up to 3.9%), increasing the probability of generalization of infection and hysterectomy to 1.3%. The negative effect of a long waterless interval on the morbidity of newborns was proved: the frequency of intrauterine hypoxia and asphyxia at birth increased 2.8 times in group 1, respiratory distress syndrome - 6.3 times, cerebral status disorders – 3 times, intrauterine pneumonia - 1.5 times.*

Keywords: *premature birth; premature rupture of fetal membranes; long waterless interval; purulent-septic diseases; complications of puerperium; morbidity of newborns*

Preterm labor (PL) complicated by premature rupture of the fetal membranes (PRFM) continues to be in the focus of attention of obstetricians-gynecologists and neonatologists, due to high rates of perinatal morbidity and mortality in the absence of a tendency to decrease them [1, 2, 3]. According to the literature, PRFM reaches 38-51% of the total number of all PL [4].

A significant importance among the etiological factors of this complication of gestation belongs to the presence of an infectious agent in the lower parts of the genital tract, which leads to subclinical intraamniotic infection and directly affects the condition of the pregnant and newborn [4, 5]. Currently, a large number of works are devoted to studying the effect of a long waterless interval on fetal development and the effectiveness of preventive measures against neonatal sepsis [4, 6, 7]. At the same time, the risk for the mother during prolongation of premature pregnancy with PRFM is primarily associated with the appearance of symptoms of chorioamnionitis (13-60%), which is an absolute indication for rapid delivery, including by caesarean section, and negatively affects the course of the postpartum period [1, 4, 8].

In accordance with modern clinical recommendations and the protocol for the management of PL with PRFM at gestation up to 34 weeks, a wait-and-see tactic should be followed with tocolytic, antibacterial therapy and prevention of fetal respiratory distress syndrome [4]. At the same time, antibiotic prophylaxis is recommended to begin immediately after the diagnosis of PRFM and continue until the birth of the child (in case of delayed delivery, it may be limited to 7-10 days). Carrying out any preventive measures in the postpartum period in this category of maternity hospitals, according to existing standards, is not provided.

It should also be noted the appearance in recent years of publications on the expediency of prolonging pregnancy with PRFM for more than 28 weeks, which does not reduce the frequency of severe neonatal infectious complications. On the other hand, according to most researchers, an increase in the waterless gap contributes to the growth of purulent-septic infections (PSI) in maternity hospitals – one of the main causes of maternal losses [3, 8, 9].

The purpose of the study: to study obstetric and perinatal outcomes of preterm labor with a long waterless interval.

Materials and methods. To achieve this goal, a single-stage cohort comparative study was conducted according to the data of the Perinatal Center of the Saratov City Clinical Hospital No. 8 for the period 2014-2015. Over a two–year period, a total of 10343 births were registered, of which 1,009 (9.75%). The 1st group included 153 patients with PL complicated by PRFM and an waterless interval of more than 12 hours, in the 2nd group (n=408) – with PL and an waterless interval of less than 12 hours. Criteria for inclusion in the 1st and 2nd groups: pregnancy with one fetus completed at gestation from 22 to 36.6 weeks, with PRFM and an

waterless interval of more than 12 hours (group 1) or with spontaneous PL with an waterless interval of less than 12 hours (group 2). Exclusion criteria: multiple pregnancy or as a result of assisted reproductive technologies, operative delivery due to severe preeclampsia, premature detachment or placenta previa, pronounced genital and extragenital pathology in the mother, congenital malformations of the fetus. The study was conducted with the approval of the Ethics Committee of the Saratov State Medical University named after V.I. Razumovsky and after receiving the voluntary informed consent of women. Examination and treatment of pregnant and maternity women in groups was carried out in accordance with the standards approved by the Ministry of Health of the Russian Federation. Anamnestic data, peculiarities of the course of pregnancy, childbirth, the postpartum period, complications of puerperium and morbidity of newborns were studied in detail.

The programs "Excel MS Office" and "Statistic 6.0" were used for statistical analysis. The hypothesis was tested for the normality of the initial data using the Kolmogorov-Smirnov criterion. The results were presented in the form of mean values (M) and standard deviation (SD). When evaluating qualitative indicators, absolute and relative frequencies of observations (n, %) were calculated. Differences between the two average values of the parameters were evaluated by the Student's t-criterion, qualitative – by the Fisher criterion $\chi 2$ (differences at $p<0.05$ were considered statistically significant).

Results and discussion. The age of the patients included in the study was in the range from 19 to 40 years, with no statistical difference in the mean age values in the groups (Table 1). At the same time, PL with PRFM and a long waterless interval (group 1) significantly prevailed during gestation up to 34 weeks, which is consistent with the current requirements of clinical recommendations [4]. And in the 2nd group, the specific weight of PL in the range from 34 to 36.6 weeks exceeded the same indicator of the 1st group by 5 times.

Table 1

General characteristics of groups

Parameter	**1st (n=153)**		**2nd (n=408)**		**p1-2**
Age, years - M (SD)	**27,8 (6,9)**		**28,5 (7,4)**		**0,94**
Distribution by gestation period					
	n	%	n	%	
22-27,6 weeks	29	19,0	2	0,5	<0,001
28-30,6 weeks	49	32,0	31	7,6	<0,001
31-33,6 weeks	53	34,6	81	19,9	<0,001
34-36,6 weeks	22	14,4	294	72,0	<0,001
Obstetric and gynecological anamnesis					
Primiparous	109	71,2	187	45,8	<0,001

Multiparous	44	28,8	221	54,2	<0,001
Premature labor in anamnesis	16	10,5	59	14,5	0,21
Abortions	8	5,2	40	9,8	0,08
Spontaneous /failed miscarriage	61	39,9	105	25,7	0,002
Inflammatory diseases of the genitals	58	37,9	173	42,4	0,34
Cervical pathology	38	24,8	66	16,2	0,02
Uterine fibroids	11	7,2	19	4,7	0,24
Infertility	18	11,8	23	5,6	0,01
Extragenital diseases					
Diseases of the blood circulation system	30	19,6	86	21,1	0,70
Diseases of the thyroid gland	29	19,0	67	16,4	0,48
Diseases of the gastrointestinal tract	39	25,5	58	14,2	0,002
Diseases of the urinary system	46	30,1	82	20,1	0,01
Chronic tonsillitis	40	26,1	73	17,9	0,03
Obesity	31	20,3	75	18,4	0,61

A detailed study of anamnestic data showed a significant predominance in the 1st group of primiparous women (71.2%; $p<0.001$). At the same time, the first pregnancy in this group was traced only in 26.1% (n=40), and in the 2nd - in 15.2% (n=62) (p=0.003). It should be noted that in terms of the frequency of induced abortions and premature labor in the anamnesis, we did not reveal statistical differences in the groups (Table 1). There was no significant difference in the incidence rates in the 1st and 2nd groups of chronic inflammatory diseases of the genitals and uterine fibroids. However, in group 1, infertility (by 2 times), cervical pathology (by 1.5 times) and spontaneous miscarriages (by 1.5 times) were observed much more often in comparison with the indicators of group 2. In addition, group 1 patients showed a statistically significant increase in the history of foci of chronic infection in the form of diseases of the gastrointestinal tract (chronic gastritis, cholecystitis, pancreatitis - 1.8 times), urinary system (cystitis, chronic pyelonephritis - 1.5 times) and chronic tonsillitis – 1.5 times (Table 1). The data obtained are consistent with the opinion of many scientists about the significant importance of chronic inflammatory diseases, genital pathology and miscarriage in the pathogenesis of PL [10,11].

When analyzing the features of the course of this pregnancy, we found no statistically significant differences in the frequency of occurrence in the groups of toxicosis of the first half, polyhydramnios, gestational pyelonephritis and anemia (Table 2).

Table 2

Pregnancy and delivery in groups

Parameter	**1st (n=153)**		**2nd (n=408)**		**p1-2**
	n	**%**	**n**	**%**	
Features of the course of pregnancy					
Toxicosis of the I half	30	19,6	86	21,1	0,70
Threatening miscarriage	79	51,6	170	41,7	0,04
The threat of termination of pregnancy in the second half of gestation	86	56,2	174	42,6	0,005
Disorders of uteroplacental blood flow	19	12,4	143	35,0	<0,001
Fetal growth retardation	12	7,8	75	18,4	0,003
Polyamnios	9	5,9	41	10,1	0,12
Oligoamnios	54	35,3	196	48,0	0,007
Isthmic-cervical insufficiency	63	41,2	129	31,6	0,03
Gestational hypertension	0	0,0	94	23,0	<0,001
Moderate preeclampsia	0	0,0	96	23,5	<0,001
Gestational pyelonephritis	23	15,0	40	9,8	0,08
Colpitis	77	50,3	78	19,1	<0,001
Chorioamnionitis	57	37,3	27	6,6	<0,001
Anemia	68	44,4	163	40,0	0,34
Acute respiratory diseases	38	24,8	49	12,0	<0,001
Delivery options and complications of labor					
Childbirth through the natural birth tract	128	83,7	161	39,5	<0,001
Anomalies of labor activity	17	11,1	96	23,5	0,002
Acute fetal distress	6	3,9	72	17,6	<0,001
Caesarean section	25	16,3	247	60,5	<0,001
Duration of waterless interval up to 12 hours	0	0,0	408	100,0	<0,001
from 16 to 48 hours	22	14,4	0	0,0	<0,001
from 3 to 8 days	75	49,0	0	0,0	<0,001
from 9 days and more	56	36,6	0	0,0	<0,001

At the same time, it was found that in group 1, pregnancy was much more frequent against the background of acute respiratory diseases (ARVI - 2 times), colpitis (2.6 times), complicated by threatening miscarriage while maintaining signs of threatening termination of pregnancy in the second half of gestation (1.3 times), the development of isthmicocervical insufficiency (in 1.3 times) and chorioamnionitis (5.7 times). While the patients of group 2 significantly increased the probability of diagnosing disorders of uteroplacental blood flow (2.8 times), fetal growth retardation (1.7 times), lack of water (1.4 times), gestational hypertension and moderate preeclampsia ($p<0.001$) (Table 2). The data obtained confirm the

existing position that the appearance of these syndromes, to a greater extent in group 2 patients, is due to morphofunctional insufficiency of the placenta, which is one of the components of the launch of spontaneous labor and termination of pregnancy [12, 13, 14]. And PL complicated by PRFM are more often associated with ascending infection of the fetal membranes and amnion [15, 16] against the background of the prevalence of foci of chronic infection, ARVI, anemia, colpitis and chorioamnionitis, which were significantly more often found in group 1.

According to our data, delivery through the natural birth canal in PL increased statistically significantly in group 1 (by 2 times, up to 83.7%) (Table 2). At the same time, violations of the contractile activity of the uterus and acute fetal distress in childbirth in this group were recorded much less frequently. And the proportion of cesarean section was 3.7 times lower than the indicator of the 2nd group.

It should also be noted that the duration of the waterless interval during PL in group 1 varied from 16 hours to 28 days. The maximum duration of prolongation of pregnancy (more than 9 days) with PRFM more often occurred at intervals of 22-27.6 weeks (86.2%) and 28-30.6 weeks (63.3%), and as the gestation period increased, there was a decrease in the frequency of using wait-and-see tactics and at 34-36.6 weeks, the time of waterless interval in most women did not exceeded 48 hours (90.9%) (Table 3).

Table 3

Duration of the waterless interval and delivery depending on the gestation period for PL complicated by PRFM

Parameter	**1st group (n=153) Gestation age (weeks)**				**p**
	22-27,6 (n=29)	**28-30,6 (n=49)**	**31-33,6 (n=53)**	**34-36,6 (n=22)**	
	1	2	3	4	
Duration of waterless interval from 16 to 48 hours, n (%)	0 (0,0)	1 (2,0)	3 (5,7)	20 (90,9)	p^{1-2}=0,44 p^{1-3}=0,19 p^{1-4}<0,001 p^{2-3}=0,35 p^{2-4}<0,001 p^{3-4}<0,001
from 3 to 8 days, n (%)	4 (13,8)	17 (34,7)	39 (73,6)	2 (9,1)	p^{1-2}=0,05 p^{1-3}<0,001 p^{1-4}=0,61 p^{2-3}<0,001 p^{2-4}=0,03 p^{3-4}<0,001

from 9 days and more, n (%)	25 (86,2)	31 (63,3)	11 (20,7)	0 (0,0)	p^{1-2}=0,03 p^{1-3}<0,001 p^{1-4}<0,001 p^{2-3}<0,001 p^{2-4}<0,001 p^{3-4}=0,02
Caesarean section, n (%)	2 (6,9)	12 (24,5)	10 (18,9)	1 (4,5)	p^{1-2}=0,05 p^{1-3}=0,14 p^{1-4}=0,72 p^{2-3}=0,49 p^{2-4}=0,045 p^{3-4}=0,11

In addition, in our study, the probability of operative delivery in PL complicated by PRFM and a long waterless interval increased statistically significantly only at the time of 28-30.6 weeks in comparison with the frequency of cesarean section during gestation periods of 22-27.6 and 34-36.6 weeks (Table 3).

Among the indications for cesarean section surgery in group 1 (n=25), the following were noted: a critical decrease in the amniotic fluid index during sonography (28%), signs of chorioamnionitis (20%) and acute fetal distress (24%) in the absence of conditions for rapid delivery, weakness of labor (20%), a combination of active labor activity in the presence of a scar on the uterus (8%). In group 2, the indications for surgery (n=247) were: anomalies of labor activity (38.1%), acute fetal distress in childbirth (29.1), scar on the uterus (11.7), placental insufficiency at the stage of sub- and decompensation in combination with fetal growth retardation of 2-3 degrees (13.4%) and chorioamnionitis (7.7%).

When studying the peculiarities of the course of the postpartum period, a higher incidence of puerperium complications in group 1 attracted attention (Table 4).

Table 4

Complications of puerperium and morbidity of newborns in groups

Parameter	**1st (n=153)**		**2nd (n=408)**		**p^{1-2}**
	n	**%**	**n**	**%**	
Features of the course of the postpartum period					
Hyperthermia	76	49,7	102	25,0	<0,001
Subinvolution of the uterus at sonography	39	25,5	69	16,9	0,02
Late hypotonic bleeding	10	6,5	2	0,5	<0,001
Infiltration of sutures on the uterus/ perineum	18	11,8	37	9,1	0,34
Endometritis	6	3,9	4	1,0	0,02
Generalization of infection (hysterectomy)	2	1,3	0	0,0	0,02

Morbidity of newborns					
Malnutrition and growth retardation	14	9,2	78	19,1	0,005
Neonatal jaundice	99	64,7	183	44,9	0,42
Intrauterine hypoxia and asphyxia at birth	121	79,1	114	27,9	<0,001
Respiratory distress syndrome	85	55,6	36	8,8	<0,001
Intrauterine pneumonia	64	41,8	114	27,9	0,002
Violations of the cerebral status	136	88,9	117	28,7	<0,001

In the group of patients with a long waterless interval, the risk of hyperthermia increased significantly in the postpartum period (by 2 times – up to 49.7%), uterine subinvolution (by 1.5 times – up to 25.5%), late hypotonic bleeding (by 13 times – up to 6.5%), endometritis (by 4 times – up to 3.9%), increasing the probability of generalization of infection and hysterectomy to 1.3%. According to the published works, PRFM should be attributed to the risk factors of infectious diseases not only in the mother, but also in the newborn [3, 10, 17, 18].

According to our data (Table 4), in group 1, such indicators of neonatal morbidity as intrauterine hypoxia and asphyxia at birth (2.8 times), respiratory distress syndrome (6.3 times), intrauterine pneumonia (1.5 times) and cerebral disorders increased significantly in relation to the parameters of group 2 status (3 times), which does not contradict existing sources of domestic and foreign literature [3, 19, 20].

Conclusions. 1. Obstetric outcomes of preterm labor with a long waterless interval are associated with an increased risk of hyperthermia (2 times), uterine subinvolution (1.5 times), late hypotonic bleeding (13 times), endometritis (4 times) in the postpartum period.

2. The negative effect of a long waterless interval on perinatal outcomes and morbidity of newborns has been proven: the frequency of intrauterine hypoxia and asphyxia at birth increases 2.8 times, respiratory distress syndrome – 6.3 times, cerebral status disorders – 3 times, intrauterine pneumonia - 1.5 times. All of the above indicates the need for further research in this area to develop a set of diagnostic and therapeutic measures to predict and prevent complications of puerperium during prolongation of pregnancy complicated by PRFM.

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THE FUNCTION OF EXTERNAL RESPIRATION IN ADOLESCENT STUDENTS OF UNIVERSITIES IN TYUMEN DURING THE COVID-19 PANDEMIC FROM THE STANDPOINT OF CHRONOBIOLOGY

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Abstract. *In conditions of forced self-isolation due to the Covid-19 pandemic, 41 students from three specialized universities in Tyumen were examined. The chronobiological study of VCL, DVCL, NRM, resistance to hypoxia according to the Stange and Gench tests in young men was performed during the day and week at 8, 12, 16 and 20 hours. It was concluded that in the period from 12:00 to 16:00 the respiratory system operates in a mode of high functionality, which should be taken into account both in the construction of the educational and training process.*

Keywords: *COVID-19 coronavirus pandemic, self-isolation, young students, breathing.*

Relevance. The Covid-19 coronavirus pandemic forced us to change the centuries-old style of teaching students and switch to distance learning, which provides for learning using the Internet at home. In this regard, many issues related to the peculiarities of the course of physiological processes in humans

due to the forced stay for a long time in a closed room, in conditions of relative physical inactivity, in conditions of a sharply narrowed information process of communication, etc., remain completely unexplored. An unresolved issue in this situation is the function of external respiration of young students of Siberian universities, who are forced to stay in conditions of relative physical inactivity and hypokinesia for a certain period of time due to self-isolation within the apartment.

The study of the health of the younger generation is the most important state task associated with the preservation of the labor, defense and intellectual potential of our country [2, 4, 6]. This is consistent with Decree of the Government of the Russian Federation № 434 "On the target project for the formation of labor potential for high-tech production" and Decree of the Government of the Russian Federation of July 24, 2000 № 551 "On military-patriotic youth and children's associations".

One of the most studied problems of modern age-related physiology, clinical and sports medicine for many years is the function of external respiration of people living in different regions of our country [7, 9]. We have not found any studies related to the chronobiological study of the function of external respiration in young students of Siberian universities who were forced to comply with the self-isolation regime due to the Covid-19 coronavirus pandemic in the available literature.

Purpose: to study the impact of restrictive measures in force on the territory of the Russian Federation during the Covid-19 pandemic on the chronobiological indicators of the function of external respiration in young students of specialized universities in Tyumen.

Material and methods. In 41 students aged 18.46±0.57 years during the Covid-19 coronavirus pandemic, a chronobiological study of the function of external respiration was performed on a voluntary basis at 8, 12, 16 and 20 hours. There were 15 (36.6%) young students of the State Agrarian University of the Northern Trans-Urals, 14 (34.1%) of the Tyumen State Medical University, 12 (29.3%) of the Tyumen State University. The assessment of the function of external respiration was performed after a 5-minute state of physical rest in a sitting position. Studied: vital capacity of the lungs (VCL, cm^3); due vital capacity of the lungs (DVCL, cm^3); the number of respiratory movements of the chest per minute (NRM, times/min); resistance to hypoxia according to the samples of Stange (s) and Gench (s). During the study, we asked the young men to go to bed no later than 23:00, wake up at 7:00 in the morning, i.e. observe the duration of sleep for 8 hours. The obtained individual data on the function of external respiration of young men were processed by statistics using the "Statistica 6.0" program. Significance of differences was determined by Student's t-test, starting from $p<0.05$.

The principles of voluntariness, the rights and freedoms of the individual, guaranteed by Articles 21 and 22 of the Constitution of the Russian Federation, as well as the Order of the Ministry of Health and Social Development of Russia №774n dated August 31, 2010 "On the Ethics Council' were observed. The study was conducted in compliance with the ethical standards set forth in the Declaration of Helsinki and the Directives of the European Community (8/609EC) and the informed oral consent of the students.

Results and discussion.

Vital capacity of the lungs. VCL was determined using a dry spirometer with an accuracy of measurement within 50 cm^3. The chronobiological determination of VCL in male students indicated that it changes in absolute values during the day and week, although there are no significant differences ($p>0.05$) (tab. 1).

Table 1

Chronobiological indicators of VCL in university students Tyumen in a state of physiological rest during daylight hours and a week (M±m)

Day of the week	Examination time				
	8 hours	12 hours	16 hours	20 hours	Averages
Monday	3.917±0.205	3.941±0.220	3.988±0.227	3.873±0.190	3.929
Tuesday	3.919±0.212	3.945±0.215	3.993±0.225	3.869±0.196	3.931
Wednesday	3.923±0.227	3.954±0.230	4.167±0.244	3.917±0.215	3.990
Thursday	3.925±0.225	3.963±0.235	4.113±0.239	3.911±0.213	3.978
Friday	3.918±0.211	3.942±0.222	4.102±0.233	3.910±0.209	3.968
Saturday	3.909±0.208	3.947±0.226	4.127±0.240	3.889±0.203	3.968
Sunday	3.903±0.207	3.940±0.219	4.090±0.238	3.877±0.189	3.952
Averages	3.9163	3.9474	4.0829	3.8923	3.959

So, the level of the average value (mesor) of VCL at 8 hours in the morning was 0.166 cm^3 higher than at 16 hours in the afternoon. The amplitude of VCL fluctuations during the day was from 3.903 to 4.167 cm^3, during the week from 3.916 to 4.082 cm^3. It is noteworthy that the VCL indicators at 8 hours in the morning, i.e. at the beginning of daylight hours, did not significantly differ from the VCL values obtained at 20:00. In absolute terms, the VCL measured at 4 pm each day of the week was higher than the VCL values obtained at 8 am and 8 pm. In addition, on Wednesday and Thursday, the VCL was higher in absolute terms than on the rest of the week. Bathyphase VCL at 8 am and 8 pm was minimal.

Due vital capacity of the lungs. DVCL was studied by calculation using the formula: DVCL = (P x 0.052) – (V x 0.022) – 4.6,

where: P – body length, cm; V – age, years; 0.052; 0.022 and 4.6 – coefficients.

We can, firstly, conclude (Table 2) that both during daylight hours and during all days of the week of being in self-isolation at home, DVCL in male students of universities in Tyumen was higher in absolute terms, although there were no statistically significant differences ($p>0.05$). Secondly, the DVCL of all young men during the day and week is greater than their VCL. Thirdly, at 4 p.m. DVCL is greater in absolute terms than at 8, 12 and 20 p.m. Fourth, the DVCL values at 8 am and 8 pm have almost the same values.

Table 2

Chronobiological indicators of DVCL in students of Tyumen universities in a state of physical rest during daylight hours and weeks (M±m)

Day of the week	Examination time			
	8 hours	12 hours	16 hours	20 hours
Monday	4.165±0.238	4.185±0.242	4.255±0.251	4.150±0.233
Tuesday	4.170±0.242	4.192±0.247	4.273±0.260	4.168±0.246
Wednesday	4.185±0.257	4.206±0.255	4.279±0.258	4.179±0.261
Thursday	4.190±0.261	4.214±0.258	4.285±0.262	4.182±0.259
Friday	4.170±0.244	4.193±0.260	4.271±0.241	4.166±0.248
Saturday	4.160±0.226	4.189±0.252	4.259±0.250	4.158±0.232
Sunday	4.155±0.223	4.182±0.248	4.252±0.254	4.151±0.239
Averages	4.171	4.195	4.410	4.164

Thus, a comparison of the absolute values of VCL and DVCL in young men indicates, albeit insignificant, but their decrease at the end of the week, which we explain by relative physical inactivity due to forced self-isolation.

Respiratory rate. For many years, the frequency and depth of respiration have attracted the attention of various researchers [5, 8], which is primarily due to safety, ease of study, and high information content. The results of the study (tab. 3) showed, firstly, that in young men studying at specialized universities in Tyumen, NRM in a state of physical rest does not go beyond age-related physiological values.

Table 3

Chronobiological indicators of NRM in students of Tyumen universities in a state of physical rest during daylight hours and a week (M±m)

Day of the week	Examination time				
	8 hours	12 hours	16 hours	20 hours	Averages
Monday	16.33±0.75	17.27±0.68	18.51±0.96	16.29±0.72	17.10
Tuesday	16.27±0.82	17.21±0.74	18.45±0.88	16.32±0.79	17.07
Wednesday	16.41±0.88	17.38±0.79	18.48±0.89	16.46±0.90	17.18

Thursday	16.38±0.79	17.35±0.77	18.63±0.94	16.31±0.68	17.16
Friday	16.40±0.83	17.53±0.80	19.12±1.12	16.38±0.81	17.35
Saturday	16.56±0.92	17.61±0.99	19.26±1.14	16.61±0.98	17.51
Sunday	16.44±0.94	17.58±0.96	18.84±1.03	16.53±0.96	17.34
Averages	16.398	17.418	18.755	16.414	17.24

Secondly, at 4 pm NRM was significantly higher ($p<0.05$) than at 8 am and 8 pm. Thirdly, NRM at 8 am and 8 pm do not have significant differences ($p>0.05$). The daily NRM amplitude during the day and week ranged from 16.27 to 18.63 times per minute.

The resistance of young men to hypoxia according to the results of the Stange test

Stange and Gench tests for the purpose of rapid assessment of the function of external respiration have become firmly established in clinical and sports practice and have taken a worthy and honorable place in it due to safety and ease of execution [1, 3, 10, 11, 12]. As a result of the study, firstly, it was found (Table 4) that the duration of voluntary breath holding on inspiration in young men from Tyumen universities in a state of physical rest during the day and week was at the level of "good" values, i.e. within 40- 60 s.

Table 4

Chronobiological indicators of the resistance of the body of young men of Tyumen universities in a state of physical rest during daylight hours and a week to hypoxia according to the results of the Stange test (M±m)

Day of the week	Examination time				Averages
	8 hours	12 hours	16 hours	20 hours	
Monday	48.2±2.4	51.5±2.3	53.6±2.6	49.3±2.2	50.65
Tuesday	48.5±2.5	51.9±2.6	54.4±2.9	49.9±2.5	51.17
Wednesday	49.4±2.4	52.2±2.5	55.3±3.2	50.2±2.4	51.77
Thursday	49.2±2.2	52.4±2.5	55.9±3.4	50.0±2.3	51.87
Friday	48.6±2.6	52.0±2.4	55.0±3.1	49.4±2.1	51.25
Saturday	47.8±2.1	51.7±2.7	54.6±2.8	48.6±2.2	50.67
Sunday	47.3±1.9	51.1±2.4	54.2±2.6	47.9±2.0	50.12
Averages	48.428	51.828	54.714	49.328	51.07

Secondly, during the day and week, the duration of the amplitude of voluntary breath holding on inspiration varied from 47.3 s to 55.9 s, i.e. its span was 8.6 s. Thirdly, the maximum breath holding during the day and the week took place at 4 pm, while the minimum duration of breath holding was found at 8 am and 8

pm, and in absolute terms, the duration of breath holding during these hours was almost the same ($p>0.05$). All young men before and after the Stange test were counted heart rate and studied the indicator of the reaction of heart rate (PR, c.u.) in response to breath holding according to the formula: PR = heart rate after the Stange test for 30 seconds / heart rate before the Stange test for 30 seconds.

It should be noted that during the day and week PR did not exceed 1.2 c.u., which we regard as a favorable reaction of the cardiovascular system to the lack of oxygen when holding the breath while inhaling.

The resistance of young men to hypoxia according to the results of the Gench test

Based on the study of the resistance of young men to hypoxia according to the Gench test, we can, firstly, conclude that in all of them it was rated as "good", because it did not go beyond 30-39 sec. (tab. 5). The results of the Gench test were evaluated by us as follows: "excellent" - more than 41 seconds; "good" - 30-39 sec.

Table 5

Chronobiological indicators of the resistance of the body of young men of Tyumen universities in a state of physical rest during daylight hours and a week to hypoxia according to the results of the Gench test (M±m)

Day of the week	Examination time				Averages
	8 hours	12 hours	16 hours	20 hours	
Monday	34.6 ± 1.9	35.4 ± 2.0	37.2 ± 2.2	34.1 ± 1.9	35.32
Tuesday	35.2 ± 2.2	36.9 ± 2.3	38.3 ± 2.3	34.8 ± 2.0	36.30
Wednesday	35.5 ± 2.4	37.2 ± 2.6	39.8 ± 2.6	35.6 ± 2.2	37.02
Thursday	35.6 ± 2.4	37.7 ± 2.7	40.1 ± 2.6	35.9 ± 2.0	37.32
Friday	34.3 ± 1.9	35.6 ± 2.1	39.8 ± 2.5	34.6 ± 1.9	36.07
Saturday	34.6 ± 1.9	35.9 ± 2.0	38.2 ± 2.4	34.4 ± 1.8	35.77
Sunday	34.1 ± 1.8	35.5 ± 2.4	38.4 ± 2.5	34.2 ± 1.8	35.55
Averages	34.84	36.31	38.82	34.80	36.19

Secondly, during the day, the maximum values of voluntary breath holding on exhalation were recorded at 16:00, while the minimum values were at 8:00 in the morning and at 20:00. The amplitude of the scatter in the duration of breath holding on exhalation ranged from 34.1 to 40.1 s, i.e. 6.0 sec. In absolute terms, the duration of breath holding was noted on Wednesday and Thursday. Before and after the Gench test, all young men were counted heart rate with the calculation of the indicator of the reaction of heart rate in response to holding the breath on exhalation according to the formula: PR = heart rate after the Gench test for 30 seconds / heart rate before the Gench test for 30 seconds.

Studies showed that during the day and week, PR did not exceed 1.2 c.u., which we regard as a favorable reaction of the cardiovascular system to a lack of oxygen during breath holding on exhalation.

Thus, based on the study, the following **conclusions** can be drawn:

1. Despite the temporary forced self-isolation due to the Covid-19 coronavirus pandemic and the relative hypokinesia associated with this, the functional state of the respiratory system and the resistance of young students of Tyumen universities to hypoxia in a state of physical rest do not go beyond the physiological norm.

2. Chronobiological study during the day and week of VCL, DVCL, NRM, the resistance of young men to hypoxia according to the Stange and Gench tests in a state of physical rest reflected their good functional state that took place before the Covid-19 coronavirus pandemic. In assessing the activity of the respiratory system in conditions of limited examination possibilities, the above tests, with their simplicity and accessibility, give an objective idea of its functional capabilities.

3. Testing the body of students in chronobiological terms during the day and week allows us to conclude that at 12 and especially at 16 pm the respiratory system operates in the mode of high functionality, which should be taken into account both in the construction of the educational and training process.

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FEATURES AND BENEFITS OF THE CARIPRAZINE USE AS A THIRD-GENERATION ANTIPSYCHOTIC IN VARIOUS MENTAL DISORDERS

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Abstract. *Cariprazine is a new generation antipsychotic, a partial agonist of dopamine D3 / D2 receptors with a predominant effect on D3 receptors. High efficacy in the treatment of patients with schizophrenia, including those with predominant negative disorders, and good tolerability of the drug have been established in a series of randomized controlled trials. Cariprazine does not adversely affect metabolic variables, prolactin levels and the QT interval. The drug may be useful for the treatment of adult patients with schizophrenia with productive and negative disorders, including those who are at high risk of metabolic and cardiovascular disorders.*

Keywords: *antipsychotic, cariprazine, partial dopamine agonist, schizophrenia.*

Antipsychotics of the third (new) generation continue the evolution of increasing the effectiveness and mitigation of side effects in the use of antipsychotics. To achieve these goals, their biochemical targets were modified. These drugs have a slightly different mechanism of action than typical and atypical antipsychotics. If the mechanism of action of neuroleptics of the first generations is to block receptors, which, of course, helped to effectively stop acute and long-term psychotic states, to carry out maintenance treatment. However, residual symptoms, a wide range of side effects, and difficulties in selecting the appropriate drug for a particular patient do not allow them to become a benchmark for the treatment of psychosis.

The difference between the new generation antipsychotics and previous generations is that instead of blocking receptors, they have partial agonism to D2- and D3-dopamine receptors, which are a weaker synthetic analogue of dopamine. Taking such drugs allows patients to reduce negative symptoms, cognitive impairment, neurological, metabolic, endocrine and other disorders, and more effectively restore the ability to live independently. In other words, the latest generation of neuroleptics have an extended spectrum of therapeutic efficacy, an improved safety and tolerability profile.

The principle of partial agonism of new generation antipsychotics is an innovative mechanism that has taken the treatment of schizophrenia to a new level by achieving the following effects:

- the effectiveness of relieving positive symptoms is comparable to first and second generation antipsychotics;
- efficiency is achieved due to the impact on the receptors of "weakened" dopamine, and not by blocking the receptors;
- therapeutic efficacy in relation to negative symptoms is determined by mild decompensation of neurotransmission in the dopaminergic system (an inaccessible effect for antipsychotics of the first and second generations);
- the risk of extrapyramidal symptoms (EPS) is minimized or, as a rule, absent;
- have a significantly improved tolerability.

Analyzing the peculiarities of metabolism and biochemical targets of third-generation antipsychotics, it is necessary to highlight the following: in third-generation antipsychotics, the dopaminergic effect is conditionally located in the spectrum of "direct D2-agonism - inverse D2-agonism". This feature made it possible to separate these drugs into a new group, referred to as "partial dopamine receptor agonists".

Partial agonists are supposed to "stabilize" dopaminergic transmission at a certain level. With an excess of dopamine in the mesolimbic system, they reduce dopaminergic transmission due to the blockade of D2 receptors, weakening the manifestations of psychosis. When it is deficient (in the prefrontal cortical zones), it is stimulated due to the "internal" dopaminergic activity of the molecule, which can be manifested by a weakening of the apato-abulic symptoms and an improvement in the cognitive sphere. Due to the limited spectrum of receptor activity of this group of drugs, they are characterized by a low risk of neurological and endocrine side effects. These features made it possible to identify partial dopamine receptor agonists in the group of third-generation antipsychotics.

Although D2 receptor antagonism was accepted as a way to control the positive symptoms of schizophrenia, a new hypothesis developed in the late 1970s began to involve effects on dopamine autoreceptors, composed of high density D2 and low density D3 receptors. When activated, they cause both decreased synthesis and

release of dopamine. The behavioral response to a drug that is a full D2 agonist is usually biphasic: inhibition at low doses of the drug (the result of autoreceptor stimulation) and stimulation at higher doses (direct postsynaptic activation). One of the main mechanisms explaining this biphasic effect is a greater presynaptic D2-like receptor pool. According to pharmacological theory, a partial agonist should be much more effective at activating presynaptic receptors when there is a high receptor pool.

Data from preclinical studies using the most valid animal models of schizophrenia suggest that the "atypicality" of modern antipsychotics is associated not only with their 5-HT2A receptor antagonism, but, perhaps even more, is determined by their ability to act as direct 5-HT1A receptor agonists; and potent antagonists/inverse agonists of 5-HT2C, 5-HT6, 5-HT7 serotonin and α2 adrenergic receptors. The role of these receptors in the regulation of prefrontal levels of dopamine and norepinephrine is shown, which, in turn, is of critical importance in the regulation of cognitive functions, motivation, and mood.

Differences in the pharmacological activity of drugs may be more profound, taking into account the characteristics of the impact at the level of secondary mediators. The existence of many active receptor conformations associated with the activation of various G-proteins and β-arrestins determines the possibility of differential regulation of independent intracellular cascades by ligands. At the same time, ligands can differ in the degree of internal efficiency (Emax) in relation to each specific pathway of intracellular signal transmission.

The data presented, indicating the complexity and multilevel interaction of pharmacological agents with the central nervous system, suggest that a deeper understanding of the mechanism of action of drugs used in clinical practice will help to identify clinical correlates of modulation of the activity of individual receptors and intracellular cascades, individualization of therapy in the future lead to the creation of drugs with improved tolerability and efficacy [1].

Of the third-generation antipsychotics, aripiprazole and cariprazine should be especially noted. Ribeiro et al. [2] summarized the results of the analysis of systematic reviews on aripiprazole and showed that the drug showed similar efficacy with first and second generation antipsychotics (with the exception of olanzapine and amisulpride) with a lower incidence of adverse events. The mechanism of action of aripiprazole is associated with either D2 partial agonism or D2 functional selectivity. Although the hypothesis of partial agonism of aripiprazole is more widely accepted, there is a point of view that the hypothesis of D2-functional selectivity can unify all data on aripiprazole, and also allows to explain the action of new compounds that are not pure D2 receptor antagonists [3].

Functional selectivity is inherent in drugs that cause different signaling through one receptor (for example, a full agonist in one pathway and an antagonist in the

second). This mechanism is considered as extremely important for patients with schizophrenia. Recent studies suggest that there may be differences in functional selectivity (primary activation of certain intracellular signaling cascades) in the somatosensory cortex between those 5-HT2A agonists that cause behavioral effects typical of hallucinogens (in particular, head nodding) in mice, and those that do not cause such effects, such as lisuride. Interestingly, those 5-HT2A agonists that do not produce these hallucinogen-typical behavioral effects in mice are also not hallucinogenic in humans, even at high doses, despite being highly potent 5-HT2A agonists. [4,5].

Cariprazine has a partial agonism to D2- and D3-receptors with a predominant effect on the latter. Being a partial agonist of D2 receptors, in this respect it is close to aripiprazole, however, its high affinity for D3 receptors (ten times higher than that of atypical antipsychotics, including olanzapine and risperidone), which is largely superior to the effect on D2 receptors, makes its receptor activity profile is unique. The uniqueness of the receptor profile of cariprazine also lies in the fact that it is the only drug that inhibits D3 receptors not only in vitro, but also in vivo in patients with schizophrenia [6]. In addition, cariprazine is a partial agonist of serotonin 5HT1A receptors, an antagonist of 5HT2B and 5HT2A receptors, and histamine H1 receptors. These properties explain the effectiveness of the drug in the treatment of negative symptoms, which is confirmed by the data of a new observational study in real clinical practice. At the 28th Congress of the European Psychiatric Association (EPA, July 4-7, 2020), new data on the effectiveness of cariprazine in the treatment of negative symptoms of schizophrenia were presented. An observational study in an outpatient psychiatric network confirmed the positive effect of cariprazine on negative symptoms in patients for whom previous therapy was ineffective. At the same time, a favorable safety profile of the drug was demonstrated. The effect of cariprazine on changes in heart rate and QT interval was minimal, comparable to placebo [7].

The EPA Congress (2020) also presented the results of a retrospective comparative analysis of the use of cariprazine and risperidone in the treatment of schizophrenia. The drugs showed comparable efficacy in relieving the general symptoms of an exacerbation of schizophrenia, but only the first showed a positive effect on the treatment of primary negative symptoms in patients in the acute phase of the disease. Cariprazine has also shown greater efficacy in the treatment of patients with predominantly negative symptoms of schizophrenia [8].

To date, cariprazine is the only antipsychotic with proven superiority in the treatment of primary negative symptoms in accordance with modern methodological requirements [9,10]. Evidence for the efficacy of cariprazine in the treatment of negative symptoms was obtained in a 26-week, randomized, double-blind, comparative (no placebo-controlled) study of cariprazine 4.5

mg/day and risperidone 4 mg/day in 460 adult patients with predominant and persistent negative symptoms [11]. This study showed a significant superiority of Cariprazine in the reduction of negative symptoms (changes in PANSS Negative Symptom Factor scores), reaching the level of significance from the 14th week and then steadily increasing until the end of the study period. In addition, an additional analysis of the data from this study showed an effective effect of cariprazine on most (5 of 7) negative symptoms assessed in PANSS (flattened affect, emotional withdrawal, passive-apathetic social withdrawal, low contact, impaired abstract thinking), suggesting a wide spectrum of clinical efficacy of Cariprazine in relation to deficient disorders in schizophrenia [12].

In addition, the use of cariprazine, unlike other antipsychotics, does not lead to the development of drug-induced hyperprolactinemia and its main symptoms - galactorrhea and amenorrhea in women, gynecomastia and sexual dysfunction in men. It has been proven that cariprazine also does not adversely affect renal function, which, along with the absence of neuroendocrine side effects, demonstrates the safety of its use [13].

Currently, cariprazine is rightly considered one of the most significant third-generation antipsychotics with efficacy against primary negative symptoms [14], with the possibility of treating not only schizophrenia, but also bipolar affective disorder [15]. The safety of the drug is evidenced by its good tolerance in adolescent and older patients [16]. The innovative characteristics of cariprazine allow for a stable qualitative remission of schizophrenia [17].

The new generation of antipsychotics, unlike the drugs of the first generation, the creation of which was largely empirical in nature, is based on the results of biochemical, neurophysiological studies of the functioning of the brain. Third-generation antipsychotics open up new possibilities in the treatment of psychosis within the framework of a personalized approach in psychiatry, providing not only the achievement of a qualitative remission of the disease, but also the prospect of functional recovery of patients [18-21].

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MICROBIOME FEATURES OF EARLY-ONSET ORAL SQUAMOUS CELL CARCINOMA BASED ON 16S RRNA PROFILING

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Abstract. *Head and neck cancer is the sixth most common cancer worldwide, affecting the oral cavity in almost half of the cases. Oral squamous cell carcinoma (OSCC) is one of the most important medical and socio-economic problems in most developed countries of the world due to the high mortality rate from this disease (about 40%) in the first year after diagnosis. At the same time, the incidence of OSCC among patients under 45 years of age is growing every year. Aggressiveness of the disease, ineffective standard treatment regimens, as well as the absence of classical etiological factors for head and neck tumors (tobacco, alcohol and human papillomavirus) are characteristics of early-onset OSCC. The aim of the study was to estimate microbiome community profile of OSCC in young adults (≤45 years) in comparison with patients older than 45 years.* ***Material and methods:*** *The material for the study was the tumor tissue of 10 patients with OSCC. Microbiome analysis was performed using 16S rRNA sequencing. Statistical analysis was carried out using the Statistica 10 software package.* ***Results:*** *At the genus level, Bibersteinia, Haemophilus, Erysipelothrix, Rubrivivax and at the species level, Haemophilus parainfluenzae were significantly enriched in tumor tissue of young adults with OSCC. Fusobacterium at the genus level and Ruminococcus gnavus at the species level were significantly increased in the tumor tissue of aged patients. Bibersteinia trehalosi has only been found in OSCC tissue of patients under 45 years of age.* **Conclusions:** *OSCC in young adults is characterized by a. The fundamental significance, the results obtained have undeniable practical value. The specific profile of microbiome community of early-onset OSCC could be used as a basis for the development of diagnostic and prognostic markers and new therapeutic targets.*

Keywords: *oral cancer, early-onset, microbiome.*

Background: Head and neck cancer is the seventh most common type of cancer worldwide, affecting the mouth in almost half of cases. Oral squamous cell carcinoma (OSCC) is one of the most important medical and socio-economic problems in most developed countries of the world due to high mortality (about 40%) in the first year after diagnosis. At the same time, the incidence of OSCC among patients under 45 years of age is growing every year [1]. Young adults with OSCC are characterized by an aggressive course of the disease, ineffective use of standard treatment regimens [2], as well as the absence of classical etiological factors characteristic of patients with head and neck tumors: tobacco use, alcohol use, and human papillomavirus infection [3].

The human microbiome is an evolutionarily developed ecological system of various microorganisms inhabiting the open cavities of the body. A modern approach for microbiome typing is metagenome analysis through massively parallel sequencing. The metagenome is the total genome of a community of microorganisms. Metagenomics makes it possible to determine the species diversity of the sample under study without the need for isolation and cultivation of microorganisms.

Microorganisms are an important link in the regulation of metabolism, immune function and human health [4]. The oral cavity is home to over 700 species of microorganisms [5]. Some of them play a key role in the development of oral diseases through the mechanisms of chronic inflammation and effects on the immune system. Periodontitis-causing taxa such as *Fusobacterium, Dialister, Peptostreptococcus, Filifactor, Peptococcus, Catonella,* and *Parvimonas* have been shown to be associated with OSCC [6], and high levels of *Prevotella melaninogenica, Streptococcus mitis*, and *Capnocytophaga gingivalis* in saliva may be a marker of OSCC [7].

In this regard, an important task is to identify the pathogenetic causes of the onset and progression of early-onset OSCC. Many studies have shown the role of the microbiome in human health and various diseases. **The aim** of the study was to estimate microbiome community profile of OSCC in young adults (≤45 years) in comparison with patients older than 45 years.

Material and methods: Two groups of patients with OSCC (T2-3N0-2M0) aged up to (n=5) and older than 45 years (n=5) were formed, who did not smoke and did not receive neoadjuvant chemotherapy. The material for the study was tumor tissue. DNA was isolated from tumor tissue samples using the DNeasy Blood & Tissue Kit (Qiagen, USA) for further amplification of 16S rDNA using a pair of primers 341F and 805R to the V3-V4 hypervariable region and sequencing in 2x250 mode on the MiSeq platform (Illumina, USA). Statistical processing of the results was performed using the Statistica 10 program.

Results: The profile of the microbiome community of OSCC in patients younger and older than 45 years was analyzed (Table 1).

Table 1

The microbiome community profile of OSCC in a group of young and old adults

Genus	Species	Fold Change	p-value
Haemophilus		4.596	0.030
Haemophilus	*Parainfluenzae*	4.245	0.015
Erysipelothrix		5.723	0.010
Fusobacterium		0.320	0.049
Rubrivivax		2.990	0.040
Ruminococcus	*Gnavus*	0.207	0.042

Note - A fold change indicates diferences between the early-onset OSCC samples and the OSCC samples of patients older than 45 years.

At the genus level we observed a significant enrichment of *Haemophilus*, *Erysipelothrix,* and *Rubrivivax* and depletion of *Fusobacterium* in OSCC tissues of young patients compared to patients older than 45 years. At the species level, *Haemophilus parainfluenzae* was significantly enriched by 4.2 times in tumors of young adults. *Ruminococcus gnavus* was observed at levels 4.8-fold higher in OSCC tissues of older patients compared to young adults. *Bibersteinia trehalosi* was found only young patients with OSCC in 60% of cases.

There was no data on the relationship of the species *Bibersteinia trehalosi, Ruminococcus gnavus* and the genus *Bibersteinia, Rubrivivax* with OSCC. Only one case report of *Erysipelothrix* bacteremia in 32-year-old males with oropharyngeal cancer was found to be associated with OSCC [8]. *Fusobacterium* dominates the healthy oral microbiota; the proportion becomes significantly higher in patients with OSCC [9]. *F. nucleatum* can induce an epithelial-mesenchymal transition program in OSCC cells sensitive to TGF-β, TNFα and EGF signaling. In vivo, *F. nucleatum* and *P. gingivalis* co-infection exacerbated tumor development in 4NQO mouse squamous tongue cancer models. The infected group had larger, more invasive tumors with increased expression of the cell cycle progression marker cyclin D1 [10]. *H. parainfluenzae* demonstrated a differential antiproliferative effect in relation to representatives of cancer cells in comparison with normal controls [11]. In this connection, there may be a secondary increase in the totality of the microorganism in response to the appearance of a tumor.

Conclusion: Early-onset OSCC is characterized by a specific microbiome community. The data obtained can serve as the basis for the development of new methods for monitoring the onset and progression of OSCC in young adults.

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THE ROLE OF WORKING CONDITIONS IN THE FORMATION OF CARDIOVASCULAR PATHOLOGY IN EMPLOYEES OF GAS DISTRIBUTION STATIONS

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Annotation. *Employees of the gas industry are exposed to adverse environmental factors on their health and the additional impact of occupational hazards. The combination of harmful industrial, hereditary and social factors contribute to the accelerated development of diseases of the cardiovascular system. This study was conducted in order to identify the role of working conditions in the formation of cardiovascular pathology in employees of gas distribution stations. The general assessment of the working conditions of the surveyed according to hygienic criteria (p.2.2.2006-05) corresponds to the harmful class - 3.1. As a result of the study, it was revealed that the presence of harmful production factors, such as: work related to the use of flammable and explosive materials, responsibility for the result of their own activities and the significance of the error, the probability of risk to their own - are a high stress factor and increase the risk of developing cardiovascular diseases*

Keywords: *working conditions, cardiovascular diseases, employees of gas distribution stations.*

The problem of early detection and prevention of production-related diseases is one of the priorities in occupational medicine. Employees of the gas industry, in addition to unfavorable environmental sources, are subject to additional effects of occupational hazards on their health. In the process of adaptation to the effects of factors of industrial activity, the body experiences functional stress, which is

characterized by the failure of factors of nonspecific protection and leads to a faster development of diseases in comparison with persons in the general population. Physiological mechanisms that cause an increase in nonspecific resistance of the body in production conditions, they act due to neurohumoral regulation. An indicator of the adaptive capabilities of the body is the cardiovascular system, the level of functioning of which is the leading indicator reflecting the balance of the body with the environment [1]. In the structure of total mortality, 55% is mortality from cardiovascular diseases. An unfavorable prognosis of arterial hypertension significantly affects the working capacity of the working population, the risk of cardiovascular catastrophes increases significantly, and the average life expectancy decreases [2]. Mortality rates from cardiovascular diseases in Russia are among the highest in the world. Cardiovascular diseases are the most common cause of hospitalizations and disability of the population of the Russian Federation. Coronary heart disease significantly limits social and labor activity in able-bodied and creatively active individuals, while there is a tendency to "rejuvenate" this pathology.

Cerebrovascular diseases occupy one of the first places in terms of overall morbidity in the world. In the structure of total mortality in the Russian Federation, acute cerebral circulatory disorders occupy the second place after hypertension and account for 21.4% [3]. The combination of harmful industrial, hereditary individual and social factors contribute to the accelerated development of diseases of the cardiovascular system [3]. In this regard, it is important to identify cardiovascular pathology at a periodic medical examination and prescribe appropriate examination and treatment for each individual patient.

The purpose of the work: to identify the role of working conditions in the formation of cardiovascular pathology in employees of Gas Distribution Stations in Ufa.

Materials and methods:

Employees of Ufa gas distribution stations were examined in the conditions of the consultative and polyclinic department of the clinic of the Ufa Research Institute of Occupational Health and Human Ecology. According to professional criteria, patients were represented by locksmiths of emergency recovery works, locksmiths for the operation and repair of gas equipment, locksmiths for the operation and repair of underground gas pipelines. The workers were engaged in work related to the use of flammable and explosive materials, in explosive and fire-hazardous industries, work at height.

Conventional clinical and laboratory methods of examination were carried out: a general blood test, urine, biochemical blood test (cholesterol, glucose), electrocardiography, according to indications - echocardiography, daily blood pressure monitoring. Patients were examined by internists, neurologists, oculists, otorhinolaryngologist, psychiatrists, narcologists, surgeons.

Conventional clinical and laboratory methods of examination were carried out: a general blood test, urine, biochemical blood test (cholesterol, glucose), electrocardiography, according to indications - echocardiography, daily blood pressure monitoring. Patients were examined by internists, neurologists, oculists, otorhinolaryngologist, psychiatrists, narcologists, surgeons.

The main contingent of employees were men in the number of 60 people, aged from 28 to 55 years; average age 39.7± 6.2. Work experience from 10 to 29 years, average work experience 10±2.3. The control group consisted of intellectual labor workers in the number of 30 people. The main and control groups were comparable in gender and age. The severity of the work of the surveyed corresponded to class 3.1. When they performed individual works, a risk to their own lives was likely (3.1). Their work was assigned to the permissible class 2 by intensity. At the same time, the general assessment of the working conditions of gas fitters by the degree of harmfulness and danger was assigned to class 3.1.

Thus, the workers of the main professions were exposed to the complex effects of harmful production factors.

Results: Employees on the basis of a medical examination are divided into three health groups. The most numerous was group III, which included those examined with chronic non-communicable diseases - 45.1%. The second health group included 38.4% of workers at risk of developing diseases. Practically healthy persons included in the I health group made up only 16.5% of employees. According to the data of periodic medical examinations (PMO), diseases of the circulatory system and musculoskeletal system predominated in the structure of previously known chronic diseases in employees of enterprises, amounting to 19.3% and 18.5%, respectively. The examined patients complained of periodic headaches, mainly in the parietal – occipital region, memory impairment, decreased sleep quality, stabbing pains in the heart area.

The examined patients complained of periodic headaches, mainly in the parietal – occipital region, memory impairment, decreased sleep quality, stabbing pains in the heart area. When analyzing outpatient cards from the place of residence and collecting anamnesis, it turned out that employees suffered from diseases of the cardiovascular system for several years, having a deterioration in their condition with a frequency of 1-2 times a year, and 5 people (8.3%) were on the temporary disability sheet over the past 2 years. There is a tendency to exceed the frequency of diseases of the circulatory system the workers of the studied production over the indicators of the comparison group. The most common nosological form was hypertension. The average age of occurrence was 40.5 years with a work experience of 10-15 years.

In this regard, it is important to identify arterial hypertension on the periodic medical examination and prescribe appropriate examination and treatment for

each individual patient. Among the examined, 18 people (30.0%) with stage 1 arterial hypertension aged 50 years and older were identified. 5 (8.3%) people suffered from coronary heart disease, including 3 (5.0%) people had a history of myocardial infarction. There is a high prevalence of neurocirculatory dystonia of the hypertensive type.

Hypertension of the second stage was diagnosed in 6 examined patients (10.0%) on the basis of generally recognized criteria. It should be noted that in half of the workers, an increase in blood pressure in combination with laboratory and instrumental signs of target organ damage was not accompanied by subjective sensations, and, as a rule, basic hypotensive therapy was not carried out. All workers with cardiovascular pathology revealed changes in the fundus in the form of hypertensive angiopathy, signs of left ventricular hypertrophy according to electrocardiography, increased blood pressure during daily blood pressure monitoring. Echocardiography revealed a tendency to increase the size of the left ventricular cavity and an increase in the mass index of the left ventricular myocardium. In a number of patients, an increase in blood pressure manifested itself in the form of a disorder of the autonomic nervous system.

A common characteristic of the work of the cardiovascular system is systolic blood pressure, the value of which, together with other factors, is greatly influenced by the volume of physical activity. The inability of the body to maintain the average dynamic pressure, one of the stable indicators of the cardiovascular system, during physical exertion is one of the early signs of a violation of the circulatory system.

Thus, the working conditions of the employees of the gas distribution stations in Ufa are not safe for the health of workers, which is due to the presence of a complex of harmful production factors of the working environment and the labor process. The general assessment of working conditions according to hygienic criteria (p.2.2.2006-05) corresponds to the harmful class - 3.1. Explosion and fire hazard of production, responsibility for the result of one's own activity and the significance of the error, the probability of risk to one's own life, are a high stress factor and increase the risk of cardiovascular diseases. In order to protect health, a set of measures for primary prevention is needed, including optimization of the labor process, careful professional selection, qualified medical control and the introduction of health measures.

Early diagnosis of production-related and general somatic diseases in employees of gas distribution stations carrying out repair work depends on the quality of periodic medical examinations. Carrying out timely medical and preventive, sanitary and organizational measures contribute to the preservation of the health of the working contingent and professional fitness.

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FEATURES OF THE MANIFESTATION OF DIFFUSE NON-HODGKIN'S LYMPHOMA (CLINICAL OBSERVATION)

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Abstract. *The article analyzes the features of the clinical manifestations of the somatic, neurological and ophthalmological status of a patient with non-Hodgkin's lymphoma. Only timely initiated adequate polychemotherapy leads to a decrease in the clinical manifestations of the disease and an improvement in the patient's quality of life.*

Keywords: *non-Hodgkin's lymphoma, clinical manifestations, hemoblastoses*

Introduction. Orbital pathology is one of the most common reasons for visiting the emergency room, occupying a significant place in the structure of ophthalmic pathological diseases. The reason for the patient's appeal is exophthalmos (true - as a result of failure of the walls of the orbit; false - in inflammatory diseases, vascular malformations, neoplastic processes, etc.) [2]. Volumetric formations of the orbit are most often caused by non-Hodgkin's lymphomas, which belong to the group of malignant tumors of the lymphoid tissue, differing from each other in morphological structure, immunohistochemical changes, genetic features, response to specific types of therapy, as well as vital prognosis [2,3]. There are B- and T-cell lymphomas, of which B-cell lymphomas are the most common (up to 85% according to the authors). A characteristic feature of these lymphomas is aggressive growth, diffuse large B-cell histological type with a 50% cure rate [1,3]. The basis of the disease is the transformation of B-lymphocytes into malignant cells (with characteristic uncontrolled aggressive growth, dispersing throughout the body), with a change in the structure of DNA. The modern available scientific

literature describes single studies of the study of patients with this nosology, the features of damage to the organ of vision, depending on the anatomical preference for the localization of the tumor process [3,4]. Men over 60 years of age are more susceptible to the disease [2,3].

Purpose of the study – to present the features of the manifestations of hemoblastosis (diffuse non-Hodgkin's lymphoma) on the example of a clinical case.

Material and methods: Clinical observation of patient R., 67 years old, who applied to the Oblast emergency ophthalmological care room of Clinical Hospital № 2 (Tyumen) with complaints of persistent pain in the left eyeball radiating to the temple and back of the head. When looking with two eyes horizontally, doubling of objects appears.

Results and discussion. Disease history. The patient considers himself ill for six months. Accidentally noticed an increase in axillary lymph nodes on both sides. Then a soft tissue formation appeared in the region of the right mammary gland. He was examined and then treated at the Oblast Cancer Center. According to the cytomorphological and immunohistochemical study of the biopsy material of the axillary lymph node and soft tissue formation in the area of the right breast, a lymphoproliferative disease with the immunophenotype of diffuse large B-cell lymphoma, CD_{20}, PAX 5, NOS, M9680? was revealed. The patient was recommended polychemotherapy (PCT), which he temporarily refused. After about 1 week, eye symptoms began to bother (pain in the left eyeball), which gradually intensified, pain in the eyeball began to radiate to the temple and back of the head, doubling of objects appeared and bulging of the left eyeball. I have not previously consulted an ophthalmologist. I did not take PCT for the disease.

Anamnesis of life. Previously worked as a construction worker. The work was associated with hypothermia and physical exertion. Two years in retirement. Past diseases: ARVI annually, hepatitis A, pneumonia, herpes infection. As a child, he suffered from measles and chicken pox. Alcohol rarely consumes (100-200 gr). Smokes 5-6 cigarettes a day. Living conditions are satisfactory, suffers from hypertension for about 10 years, takes losartan, asparkam, corvalol, nicotinic acid.

Ophthalmological examination results: Vis 1.0/0.7-0.8 does not correct. Tp is normal (both eyes). OD - no features. OS - there is a painless, mild swelling of the eyelids, skin of physiological color, exophthalmos, displacement of the eyeball outward (dev - 350), restriction of the movement of the eyeball upward, inward, outward, conjunctival injection of the eyeball, mucous discharge from the conjunctival cavity (fig. 1). Moderate chemosis of the conjunctiva, more at the outer corner of the eyeball. The cornea is transparent, the anterior chamber is of medium depth, the moisture is transparent, the pupil is 3.5 mm, d=s, the reaction to light is live, the fundus reflex is pink. On the fundus: the optic disc

without features - with clear boundaries, pink; the arteries of the retina are sharply narrowed, sclerosed, the veins are narrowed, tortuous, the symptom of Salus-Gunn II (b) is determined (according to V. N. Arkhangelsky, 1960), the macular zone and the periphery are without pathology.

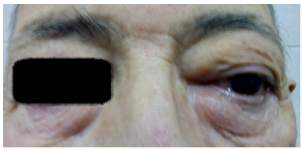

Figure 1. *Photo of patient R., 67 years old (there is a displacement of the left eyeball, exophthalmos)*

Laboratory research methods showed the presence of thrombocytopenia (170 x 10^9/l.) according to the general blood test. Instrumental research methods (CT of the brain and orbits). CT scan data of the brain. CT signs of the formation of the left orbit with exophthalmos (intraorbitally volumetric formation of heterogeneous density intimately adjacent to the lower, medial, lateral, rectus muscles, optic nerve) were revealed. Approximate size 25x22x21mm, pushes the left eyeball forward.

Neurologist's consultation. Diagnosis: Syndrome of cephalgia, ophthalmology against the background of volumetric formation of the left orbit. Relief of the pain syndrome with non-narcotic analgesics, antitumor chemotherapy in OCC by an onco-ophthalmologist was recommended.

Diagnosis. S 83.3. Diffuse large B-cell lymphoma III stage variant with lymphoid markers CD_{20}+, PAX 5+, with damage to the axillary lymph nodes on both sides and extranadal lesion - tumor of the left orbit2, soft tissue formation in the right breast. Complication. Exophthalmos of the left eye. Syndrome of cephalgia, ophthalmology. Concomitant disease. AG II deg.

Conducted emergency treatment.

Relief of pain syndrome (cephalgia, ophthalmology).

1. Dexamethasone 8 mg in 100 ml of 0.9% saline intravenously by drop (once).
2. Ketarol 2.0 ml IM (once).
3. Diakarb 0.25 mg - 1 tab. inside.

After 1 hour of observation, the patient's condition improved, pain in the left eyeball stopped. Recommendations are given for further treatment of the disease by an onco-ophthalmologist at the Oblast Oncology Center. Observation by a neurologist about pain in the left eyeball. A conversation was held about the need for urgent antitumor treatment and the continuation of analgesic therapy in a hospital setting.

Among neoplastic processes, non-Hodgkin's lymphomas are the most common cause of orbital damage (up to 36%). Orbital involvement is more common in men over 60 years of age, while conjunctival involvement is more common in women at a younger age (median age 50 years). The described clinical case is of interest to ophthalmologists, neurologists, and hematologists. In the event of exophthalmos (with displacement of the eyeball and restriction of movement) in men, with conjunctival damage (chemosis and conjunctival injection), good functional indicators (Vis 0.7-0.8) at the age of 60 years and older, one of the causes of the disease may be Non-Hodgkin's lymphoma, requiring specific treatment by an onco-ophthalmologist and a chemotherapist. Only a simultaneous approach, understanding by the patient of the cause of the disease and the need for cancer treatment, can lead to an improvement in the somatic and local ophthalmological status. Ophthalmologists in the office of emergency ophthalmic care need to be alert for this disease.

Conclusions. This clinical case shows that in men aged 60 years and older, the appearance of exophthalmos with good functional indicators of visual acuity, one of the causes of the disease may be non-Hodgkin's lymphoma.

Non-Hodgkin's lymphomas are characterized by heterogeneity and "universality" of symptoms, patients are unaware of the lesion and take pain symptoms for other diseases.

Competent diagnostics is important to distinguish this pathology from other cases, a multidisciplinary approach to the management of this category of patients.

Only timely initiated adequate therapy, in this situation, chemotherapy, leads to a decrease in ophthalmic manifestations.

This clinical case is of interest to outpatient specialists (ophthalmologists, neurologists, hematologists), since only an integrated approach to the diagnosis and treatment of this pathology can guarantee a favorable prognosis and improve the patient's quality of life.

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POSSIBILITIES OF THE FLOW CYTOMETRY FOR THE DETECTION OF B-LYMPHOCYTES IN PATIENTS WITH MULTIPLE SCLEROSIS AFTER THE USE OF VARIOUS THERAPY REGIMENS

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Abstract. *The article presents the results of the analysis of the parameters of adaptive cellular immunity, in particular, the immunophenotypic features of peripheral blood B-lymphocytes in patients with various types of multiple sclerosis (MS), after various courses of DCCMS and who were subsequently planned to be treated with MAB drugs (Ocrelizumab, Alemtuzumab). The features of cytometric analysis of B-lymphocytes are described. It was found that a significant decrease in the content of the effector and NKT subpopulations of T-lymphocytes indicates an insufficient killer potential of adaptive T-cell immunity. The persistence of a significant increase in the expression of CD25 and CD38 on B-lymphocytes after therapy with Natalizumab and IF-β may indicate a high activation potential of these cells in circulation, and, consequently, a pronounced risk of disease recurrence.*

Keywords: *Multiple sclerosis, adaptive immunity, B-lymphocytes, flow cytometry.*

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system. The main goal of MS therapy is to prevent the progression of the disease and the increase in disability. According to recent data, B cells that synthesize antibodies, present antigens to T lymphocytes, and produce cytokines that act as inflammatory mediators are considered as the central component of MS pathogenesis (1, 3, 4). Ocrelizumab (an anti-CD20 monoclonal antibody (MAB) drug) approved for the treatment of MS results in rapid removal of B cells from the blood, but the extent of B cell depletion and the kinetics of B cell recovery in different immune compartments is poorly understood (2,4). In this regard, it seems particularly relevant to study the initial parameters of B-cell immunity in patients with MS who are candidates for MAB therapy.

Materials and methods. The parameters of cellular immunity in patients with MS were assessed by 6-color flow cytometry using the MAB panel (Becton Dickinson, USA) to differentiation antigens of peripheral blood lymphocytes (PB). We studied the population and subpopulation composition of lymphocytes within the lymphocyte gate (CD45+): CD3+, CD19+, CD20+, CD3-CD16+CD56+, CD3+CD4+, CD3+CD8+, CD3+HLA-DR+. The subpopulation composition of B lymphocytes (B1 cells, memory B cells), expression of costimulatory and activation antigens (CD40, CD25, CD38, CD95) were determined within the CD19+/SSC gate.

One of the objectives of the study was to study the recovery time and immunophenotypic features of B-lymphocytes after treatment with MAB drugs (Ocrelizumab and Alemtuzumab). It was assumed that not all patients 6 months after treatment with ocrelizumab and alemtuzumab could detect B-lymphocytes in the cytometric analysis of the entire lymphocyte population - in the CD45 gate against the side scatter channel (SSC), and indeed, in most patients, CD19+ cells were absent. In this regard, we applied the method of concentration of cellular elements: PB samples were preliminarily poured into several portions in a volume of 500-1000 μl, erythrocytes were lysed (PharmLyse lysing solution (Becton Dickinson, USA), washed twice with a solution of phosphate-buffered saline (PBS) and concentrated the precipitate in one test tube. Next, PB samples were incubated at room temperature for 30 min in the dark with monoclonal antibodies (MAB) of certain specificity conjugated with fluorescent dyes in various combinations. Detection of B-lymphocytes was carried out by expression of CD19+ against SSC, at least 500,000 events were included in the analysis.

The study included 27 patients with various types of MS who received courses of Drugs that Change the Course of MS (DCCMS) and who were subsequently planned to be treated with MAB drugs (Ocrelizumab, Alemtuzumab). Patients were divided into 3 groups depending on the type of previous DCCMS therapy: 8 (29.6%) patients received interferon-β (IF-β) therapy; 11 (40.7%) patients received Natalizumab, 5 (18.5%) patients were treated with Teriflunomide. 3 patients (11.1%) did not receive DCCMS therapy. The period without DCCMS courses before the start of the study of immunological parameters was on average 5.8 months. The results of 10 donors examined for similar indicators were used as reference values.

Results. The indicators of cellular immunity of MS patients are presented in table 1.

Table 1

Cellular Immunity Scores in Multiple Sclerosis Patients (% Cells Within CD45+ Lymphocyte Gate)

Indicator, % cells	After courses of Natalizumab	After courses of IF-β preparations	After courses of Teriflunomide	Donors
	N=11	N= 8	N= 5	N=10
CD3+	72,14 +- 3,66	74,36 +- 0,97	72,50 +- 1,73	74,97+-1,53
CD3+CD4+	44,58 +- 3,54	49,11 +- 2,49*	46,57 +- 2,81	40,69 +- 2,27
CD3+CD8+	25,28 +- 2,21*	21,82 +- 1,50*	24,71 +- 2,02*	33,00 +- 3,08
CD3-CD16+CD56+	12,78 +- 1,72	9,75 +- 1,54	11,70 +- 1,15	12,47+- 1,70
CD3+CD16+CD56+	4,22 +- 0,98*	4,85 +- 1,18*	4,38 +- 2,30*	10,50 +- 1,73
CD3+HLA-DR+	8,18 +- 0,88*	7,24 +- 1,35*	8,58 +- 2,01	13,30+- 2,60
CD19+	14,20 +- 2,21	14,88 +- 1,19	14,37 +- 1,53	11,79 +- 1,86
CD20+	12,58 +- 2,07	13,75 +- 1,07	10,53 +- 4,79	11,19 +- 1,83
CD95+CD19-	41,50 +- 1,98	33,52 +- 6,24	44,37 +- 4,65	42,14 +- 6,33
CD25+CD19-	16,29 +- 3,67	20,28 +- 3,49*	28,87 +- 6,21*	11,16 +- 1,74

Note: * - differences are statistically significant compared to reference values

In all groups of patients with MS, the content of T-, B-, natural killer lymphocytes (NK) did not differ from the reference values. The content of CD20-positive B-lymphocytes was comparable to the total level of CD19+B-lymphocytes PB. For all groups of patients, a significant decrease in the content of effector (CD3+CD8+) ($p<0.05$) and NKT subpopulations of T-lymphocytes (CD3+CD16+CD56+) ($p<0.01$) was revealed. The content of the subpopulation of T-helper lymphocytes (CD4+) was significantly ($p<0.01$) increased only in the group of patients who received IF-β preparations. In patients treated with Natalizumab and IF-β, a significant ($p<0.05$) decrease in the level of activated T-lymphocytes (CD3+HLA-DR+) was observed, and in groups of patients after treatment with IF-β and Teriflunomide, a pronounced ($p< 0.05$) an increase in the expression of the IL-2 receptor (CD25) on T- and NK-lymphocytes compared with normal values.

Parameters of B-cell immunity in MS patients are presented in Table 2.

Table 2.

Scores of B-cell Immunity in Multiple Sclerosis Patients (% of Cells Within CD19+ B-Lymphocyte Gate)

Indicator, % cells	After courses of Natalizumab	After courses of IF-β preparations	After courses of Teriflunomide	Without DC-CMS Therapy	Donors
	N=11	N= 8	N= 5	N= 3	N=10
CD40+	51,65+- 8,09	69,40 +- 6,02*	55,67 +- 7,12	67,35+- 10,48*	49,20 +- 4,45
CD95+	26,49 +- 4,36	14,25 +- 4,44	22,93+- 9,78	18,82 +- 5,58	19,89 +- 2,3
CD5+	11,35 +- 2,76	17,46 +- 1,61	8,45 +- 0,83*	16,57 +- 8,64	17,29 +- 3,96
CD27+	32,08 +- 4,6	32,53 +- 5,27	25,00 +- 4,76	29,50 +- 6,90	28,30 +- 2,74
CD38+	43,00 +- 5,28*	29,34 +- 4,23*	24,83 +- 11,56	31,40 +- 7,22*	16,10 +- 2,63
CD25+	23,13 +- 3,60*	12,49 +- 1,77	29,73 +- 8,71	17,70 +- 5,19	13,79 +- 2,52

Note: * - differences are statistically significant compared to reference values

A pronounced increase in the expression of the costimulatory CD40 molecule on B-lymphocytes was found in newly diagnosed patients without DCCMS therapy ($p<0.05$) and in the group after treatment with IF-β drugs ($p<0.01$). There was a significant decrease in the content of B1-lymphocytes (CD5+ CD19+) in the group of patients treated with Teriflunomide ($p<0.05$) compared with other patients and donors. There were no significant differences in the content of memory B cells (CD27+CD19+) and B-lymphocytes expressing CD95 (a marker of readiness for apoptosis) in all MS patients compared with donors.

We recorded the most pronounced increase in the expression of activation antigens CD25 ($p<0.05$) and CD38 ($p<0.0001$) on B-lymphocytes in patients after Natalizumab therapy, as well as a significant increase in CD38 expression in patients treated with IF-β ($p<0.01$) and patients without DCCMS ($p<0.05$).

Conclusion.

1. In patients with MS who are candidates for therapy with MAB (anti-CD20) ocrelizumab, there was no decrease in the number of B-lymphocytes expressing CD20, which could be an unfavorable factor for such therapy.

2. A significant decrease in the content of effector (CD3+CD8+) and NKT subpopulations of T-lymphocytes (CD3+CD16+CD56+) indicates an insufficient killer potential of adaptive T-cell immunity.

3. A low degree of activation of T-lymphocytes by the expression of HLA-DR was noted, but a pronounced activation by the expression of CD25 (R-IL-2).

4. There was no significant increase in the content of the B1-lymphocyte subpopulation with the CD19+CD5+ phenotype associated with the production of autoAT and autoimmune pathology.

5. Pronounced expression of the co-stimulatory CD40 molecule on PB B-lymphocytes in patients without treatment and after IF-β, as well as maintaining a significant increase in the expression of CD25 and CD38 on B-lymphocytes after therapy with Natalizumab and IF-β, testify to the high activation potential of these cells in circulation, and, consequently, to the presence of a pronounced risk of developing relapses of the disease.

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INCREASING THE EFFICIENCY OF THE WRIST DEVICE FOR NON-INVASIVE MONITORING OF BLOOD GLUCOSE AND OTHER PARAMETERS OF THE HUMAN BODY BY BLOOD

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Annotation: *The article describes modern methods of non-invasive monitoring of glucose levels in human blood, as well as monitoring of other blood characteristics, such as blood pressure, oxygen saturation, etc. Promising foreign, domestic and own developments are also presented in the article.*

Keywords: *blood, blood cells, photoplethysmography, smart watches, matrix determinant, blood velocity, glucose level, blood composition, linear relations, optics, LED, monochrome radiation, coherence.*

INTRODUCTION

Monitoring the health state of people suffering from diabetes mellitus, heart and vascular diseases is crucial in therapy. There are many non-invasive glucose meters based on "smart watches", the main disadvantage of which is the longtime of preparation and implementation of non-invasive monitoring of human blood glucose levels, as well as other blood parameters. The authors of the article propose technical solutions to reduce the preparation time and the implementation of non-invasive monitoring of human blood glucose levels by preventing the movement of a mobile device on a person's hand.

Health monitoring is of great importance in the lives of people suffering from diabetes mellitus, heart and vascular diseases. For such people, a vital necessity is the constant monitoring of glucose in the blood, as well as other parameters of

the body by blood. For this purpose, non-invasive glucose meters based on "smart watches" are currently used, which determine health parameters without blood sampling and the use of test strips /1-29/.

There are many non-invasive glucose meters based on "smart watches". All of them contain a non-invasive sensor based on infrared light with a broadcast function. The sensor includes an emitter and a receiver of radiation reflected from human tissues and is connected to a microprocessor.

A non-invasive blood glucose sensor of this type refers to systems for determining the concentration of glucose in the blood based on the optical method, as well as various physiological parameters, including oxygen saturation in the human body, pulse rate, etc.

The best of modern non–invasive glucose meters is a device based on a "smart watch" for monitoring the pulse wave signal, determining blood sugar and other blood parameters with the function of manually determining the position of the radial artery and pointing the sensor at the artery. Such a device contains a control module with a microprocessor, a monitor, a strap with a mobile unit that can move along the strap and contains an infrared sensor.

A mobile unit with an infrared sensor is located above the radial artery on the wrist and is connected to the control and display module via a communication channel.

Figure 1 shows a general view of a non-invasive glucose meter based on a "smartwatch". ***Figure 2*** schematically shows the inside of the non-invasive blood glucose meter on a person's hand.

Figure 1. *A non-invasive glucose meter based on a "smart watch".*

The figure shows: 1 – monitor; 2 – sensor with infrared emitter and receiver; 3 – strap.

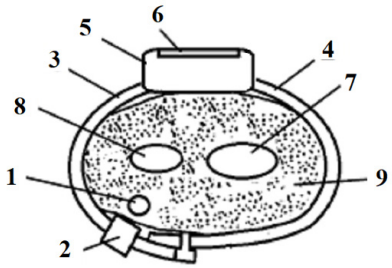

Figure 2. *A non-invasive glucose meter based on a "smart watch" on a person's hand.*

The figure shows: 1 – radial artery; 2 – sensor with infrared emitter and receiver; 3, 4 – strap parts; 5 – control and display module; 6 – monitor; 7 - ulna; 8 - radial bone; 9 – human hand tissues.

The disadvantage of all modern non-invasive glucose meters, including the best of them, is the relatively long preparation time and implementation of non-invasive monitoring of glucose in human blood, as well as other blood parameters.

How does the best modern non-invasive blood glucose meter work?

The device is tightly attached with a strap to the wrist of the left or right hand, so that the mobile unit is against the radial artery in this place of the hand. The emitter located in the mobile unit is directed at the radial artery.

A person sits motionless for 2-3 minutes, his breathing and pulse are equalized, after which he turns on the device. To do this, connect to a power source and turn on the control module by pressing buttons on the touch screen of the display. The control module verifies the correctness of the location of the mobile unit emitter relative to the radial artery. The check time is up to 3 minutes. If the location of the emitter of the mobile unit is not correct, a message about the need to re-install the emitter is displayed on the screen. The device is turned off. The strap is loosened, the mobile unit with the emitter is put on the radial artery, then the strap is tightened, tightly pressing the mobile unit to the wrist. The person sits motionless for 2-3 minutes, after which he turns on the device. Work on installing the mobile unit continues until a message appears on the display that the device is ready for operation.

When testing the best non-invasive glucose meters (**ACCOFRISK Elite** and **ACCOFRISK Pro**), it was found that the initial setup of the device for operation on average requires at least 3 attempts. Each attempt takes up to 5-6 minutes.

Figure 3 shows the options for pointing the sensor at the artery. ***Figure 3a*** shows the case when the emitter is in the working position - pointed at the radial

artery. ***Figure 3b*** shows an option when the emitter is shifted relative to the working position. It is required to re-point the sensor at the artery.

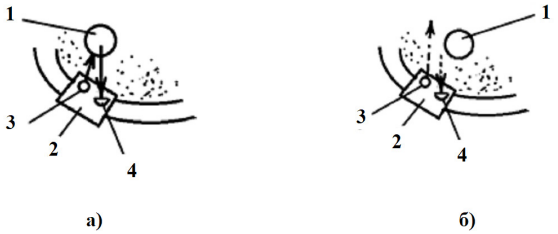

Figure 3. *Pointing the emitter at the radial artery.*
a – the emitter is in the working position - aimed at the radial artery;
b – the emitter is displaced relative to the working position.

The figure shows: 1 – radial artery; 2 – mobile unit with infrared emitter 3 and receiver 4.

After that, the device is on the person's hand in readiness to measure the level of sugar and other blood parameters. Thus, the time of the first measurement takes up to 18 minutes.

However, the described best non-invasive glucose meters have a drawback, which is as follows.

During the day, while walking and working with hands, the mobile unit and, in general, the smart watch, are shifted from the established initial position. The orientation of the sensor to the artery is shifted (loot at ***Figure 3b***).

In this case, in order to carry out the measurement, it is necessary to re-perform the operations of placing the mobile unit in the initial position for measurements. A person usually works intensively with his hands during the day. The wrist device, at the same time, shifts from its original place.

During the day, a diabetic has to repeatedly (up to 10 times or more) measure the sugar content in the blood. At the same time, it is necessary to set the mobile unit to its original position as many times and adjust the wrist device to work.

This is up to 3 hours for measurements per day with 10 measurements. The reason is the rotation of the wrist device with a strap and a mobile unit relative to the wrist and radial artery.

To eliminate the disadvantage described above, the authors of the article propose to make the strap parts with increased and decreased hardness on the strap of a wrist device, namely on the inner surface of the strap (the surface turned to the human body) (look at ***Figure 4*** and ***Figure 5***).

During the research, recesses were made in a flexible plastic strap, which have the shape of rectangles. Inserts made of soft rubber and harder plastic were placed in these recesses. Alternatively, inserts were made of rubber with different hardness.

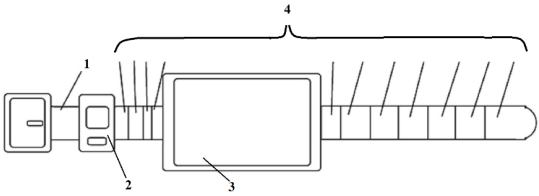

Figure 4. *Wrist device for non-invasive monitoring of blood glucose and other parameters of the human body by blood.*

On the inner surface of the strap 1, areas 4 with increased and decreased hardness are made.

The figure shows: 2 – mobile unit with infrared emitter and receiver; 3 – the inner surface of the wrist device.

Figure 5. *Wrist device for non-invasive monitoring of blood glucose and other parameters of the human body by blood.*

Areas 3, 4 and 5 with increased and decreased hardness are made on the inner surface of the strap.

The figure shows: 1 - wrist device monitor; 2 – mobile unit with infrared emitter and receiver.

More detailed information about the conducted research and the developed device is given below. The developed wrist device for non-invasive monitoring of blood glucose and other parameters of the human body by means of a strap is tightly fastened on the wrist of the left or right hand of a person, so, that the mobile unit and the sensor are against the radial artery in this part of the arm. To do this,

you need to get the pulse of the artery and press the mobile unit to this pulse point, and then tighten the strap. In this case, the emitter located in the mobile unit is directed at the radial artery.

Further actions.

A person sits motionless for 2-3 minutes or more if he worked intensively before, after which he turns on the device: turns on the power supply and turns on the control module by pressing buttons on the touch screen of the display.

After that, the control module verifies the correctness of the location of the mobile unit (emitter) relative to the radial artery. The check time is up to 3 minutes. If the location of the mobile unit is not correct, a message about the need to re-install the mobile unit is displayed on the screen

To re-install the mobile unit, the device is turned off. The strap is loosened, the mobile unit is re-exposed over the radial artery, then the strap is tightened, tightly pressing the mobile unit to the wrist. The person sits motionless for 2-3 minutes, after which he turns on the device. Work on installing the mobile unit continues until a message appears on the display that the device is ready for operation. When testing the device, it was found that the initial setup of the device for operation occurs, on average, with 3 attempts. Each attempt takes from 5 to 6 minutes in time – this is the arithmetic mean of the time out of 100 attempts made by 10 testers. After that, the device is on the person's hand in readiness to measure blood sugar levels and other parameters. Thus, the time of the first measurement takes up to 18 minutes (also the arithmetic mean of the time of 100 attempts).

As noted above, the modern non–invasive blood glucose meter has a drawback - during the day, while a person is walking and working with his hands, the mobile unit shifts from its original place. In this case, in order to carry out the measurement, it is necessary to perform operations to set the mobile unit to the initial position for measurements.

A person usually works intensively with his hands during the day. Due to this, the device shifts from its original place – turns around the wrist. During the day, a diabetic has to repeatedly (up to 10 times or more) measure the sugar content in the blood. At the same time, it is necessary to set the mobile unit to its original position as many times and configure the device to work. And this is up to 3 hours for measurements per day. This data was obtained from the results of experiments during the development of a new device for non-invasive monitoring of blood glucose and other parameters of the human body by human blood. The main reason is the rotation of the device with the strap relative to the wrist and artery.

It would seem that the problem can be solved by making the strap tighter. However, in this case, a person feels extremely uncomfortable. You can also apply glue – glue the device with a strap to your wrist every day. However, such a

solution to the problem creates discomfort for people during the day. It has a negative effect on human skin. During the research, the authors tested the above-described methods of fastening the device in practice.

The authors propose to make parts with increased and decreased hardness on the strap - on its inner surface, that is, to make a strap with variable hardness of the inner surface along the length of the strap.

During the research, parts with variable hardness were performed in two ways – by inserts of materials with different hardness and by heat treatment of parts on the inner surface of the strap. For example, in a flexible plastic or rubber strap, recesses were made that have the shape of rectangles. Inserts made of soft rubber and harder plastic were placed in these recesses.

Also, inserts of rubber with different hardness were made.

When tightening the wrist strap, the softer parts on the inner surface of the strap that fit closely to the wrist are pushed through by the wrist (pushed through by the wrist tissues). Harder parts on the inner surface of the strap that fit closely to the wrist, push through the wrist (push through the wrist tissue). This creates a reliable (with increased resistance to turning relative to the wrist) grip of the wrist with the strap.

The authors made plastic, rubber and leather straps. In the straps, the recesses for the inserts were made with a cutter. It is preferable to make rubber and plastic straps.

Inserts with reduced hardness were made from various grades of rubber. Inserts with increased hardness were made of various plastics or hard rubber. In addition, the option of manufacturing plastic and rubber straps by heat treatment of parts on their internal surfaces has been tested. Heat treatment of plastic and rubber products or their elements is widely used nowadays. So, during the development of the device, well-known methods of hardening plastics were used to create parts with minimal hardness. The required hardness characteristics of the parts were achieved by the level of heating temperature, heating speed, holding time and cooling time (rapid cooling). We achieved a local increase in the hardness of the strap by 200% of the initial hardness of the inner surface of the strap. To create areas with maximum hardness, well-known methods of annealing plastics were used. The required hardness characteristics of the areas were achieved by the level of heating temperature, heating speed and cooling time (very slow cooling).

Experiments have shown that the solution found by the authors completely eliminates the re-configuration of the device and the mobile unit during the day. A reduction in the preparation time and the implementation of non-invasive monitoring of glucose in human blood is achieved by preventing the movement of the mobile unit along the hand relative to the radial artery at the base of the thumb of the human hand.

In the experiments (10 testers participated), the time for measuring blood glucose levels was reduced by 2.3 times (with ten measurements per day) and 2.6 times (with twenty measurements per day).

It has been experimentally established that it is advisable to make parts with a maximum shore hardness value of 88, 91, 105, 146 and 154 units on the inner surface of the strap. The minimum value is 32 - 68 shore hardness. Other ratios of minimum and maximum hardness of the areas on the strap are also possible.

In the experiments, the corrugation of the surface of the device body was additionally tested to increase the effect in order to enhance the technical result.

Alternating protrusions and recesses or riffles are made on the inner surface of the device body of the wrist device that fit closely to the surface of the hand at the base of the thumb of the human hand in the transverse direction, as well as alternating protrusions and recesses or riffles are made on the surface of the device body that fit closely to the surface of the hand at the base of the thumb of the human hand in the longitudinal direction.

This strengthens the grip of the device body with the wrist, helps to prevent the movement of the device body, mobile unit together with the strap along the wrist relative to the radial artery at the base of the thumb of the human hand. At the same time, the time of preparation and implementation of non-invasive monitoring of glucose in human blood is reduced. This technical solution can be additionally applied to enhance the technical effect. In addition, this solution simultaneously promotes increased heat exchange between the device body and the wrist.

Furthermore, the authors have developed a unique design of a mobile unit with an infrared emitter and receiver. The emitter and receiver are located in a ball joint fixed in the mobile unit (look at ***Figure 6***).

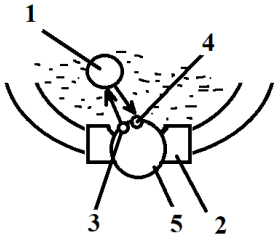

Figure 6. *Mobile unit with sensors in a ball joint.*

The figure shows: 1 – radial artery; 2 – mobile unit with infrared emitter 3 and receiver 4; 5 – ball joint for emitter and receiver.

The new design of a wrist device for non-invasive monitoring of blood glucose and other parameters of the human body differs favorably from traditional schemes in that when pointing the emitter at an artery, it is not necessary to repeat-

edly relax the strap and move the wrist device on the wrist. It is enough to rotate the ball bearing with sensors with your fingers until the emitter is pointed at the artery.

With the introduction of this design, it is also planned to reduce the time of the operation to direct the emitter to the artery.

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ACTIVATION OF THE BOND CURING SYSTEM AND DIRECTIONS FOR THE IMPLEMENTATION OF PROCESS B CONSTRUCTION PRODUCTION

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Abstract. Introduction: *The paper studies hardening activation with regard to binding systems (cements) and justifies the possibility of its implementation in construction engineering to prepare construction mixes when erecting buildings and structures out of cast-in-situ concrete and reinforced concrete. During hardening of binding systems (cements), hydrated cement phases are formed and the substance becomes solid, affecting the formation of cement stone and its strength.* ***Purpose of the study:*** *We aimed to study the mechanism of phenomena that occur during activation and hardening in binding systems as well as explore the possibility of their implementation and boosting in order to improve the physical and mechanical, processing, and performance properties of construction mixes.* ***Methods:*** *The properties and stability of binding (cement) systems, which are lyophilic systems, qualitatively characterize the interaction between a solid body and a fluid. The lyophilic behavior implies good wetting, low interfacial tension, and resistance of the surfaces to mutual adhesion.* ***Results:*** *A holistic approach to studying the mechanism of hardening activation in binding systems at the level of colloidal chemical phenomena as well as the energy of interaction between the binder and water in construction mix preparation will make it possible to determine the main directions of boosting the processes in binding systems through various types of energy impacts: mechanical, chemical, non-reagent, ultrasonic, electrostatic, and other methods.*

Keywords: *Activation, liquid phase, binding systems, cement stone, colloidal chemical phenomena, electrical double layer (EDL).*

Introduction

Since construction sites require high-quality concrete mixes, concrete mix preparation is the most critical procedure in concreting. To enhance the quality of

concrete mixes, we need to continuously seek new reserves and opportunities to improve their properties and concreting quality.

In-depth studies on the mechanism of phenomena that occur during activation in binding systems (which, in certain physical conditions, set and harden, thus forming artificial stone as a result of chemical interaction between the initial components and their physical and chemical transformations) will allow us to determine possible directions of their implementation to prepare concrete mixes in order to improve their physical and mechanical, processing, and performance properties.

We are aware of numerous projects and studies on the activation of construction mix components. Researchers studied changes in the properties of mixes upon strengthening of the cement stone crystal hydrate structure, the energy of interaction between the binder and water in construction mix preparation, and the impact of external force fields on mixing water in order to improve cement stone strength characteristics (Judina, 2019; Judina and Verstov, 2013; Zubrilov, 1989).

An analysis of activation methods shows that theoretical models and interpretations of phenomena that occur in binding systems (cement/water) have not been studied sufficiently and are often contradictory. The extensive practical application of these methods in construction (specifically, at construction sites) is restrained by volatile results in concrete strength improvement, the use of sophisticated equipment for the activation of construction mix components, and large energy consumption, which ultimately increases the cost of the end product (Yudina, 2019).

Materials and methods

A binding system is initially a system of equally important components: a solid constituent, which is cement (a binder), and a liquid constituent, which is a grouting fluid (mixing water). Due to particular chemical and physical phenomena, these components are adhesive and can harden and transform into a stone-like body (artificial stone).

The hardening of binding systems is characterized by a chemical reaction of binding the grouting fluid (mixing water) with the phases of the binders and fillers, followed by the formation of reaction products (hydrate formation) as well as the formation of a spatial framework of the hardening structure and its strengthening (structure formation).

The activation of binding systems (cement + mixing water) can be ensured by various methods: physical, physical and chemical, mechanical, etc. These methods can affect both individual components (e.g., activation (impact) of cement only or activation (impact) of mixing water only, etc.) and the system in general (cement + mixing water) (Judina, 2019; Judina and Verstov, 2013; Yudina, 2019; Zubrilov, 1989).

During hardening of binding systems (cements), hydrated cement phases are formed and the substance becomes solid, affecting the formation of cement stone and its strength. These phenomena occur in parallel. When the liquid phase interacts with cement minerals, the induction period of reaction retardation is observed. This period provides conditions for the cement/water system paste-like state and makes it possible to form required products out of construction mixes. The colloidal chemical characteristics of the paste-like state play an important role both in hardening and when making cement-based materials (water/ cement ratio, rheology, stone strength, etc.). The interaction intensity as well as the colloidal chemical properties of construction mixes are considerably predetermined by the characteristics of cement grains and the physical and chemical properties of the liquid phase.

Results and discussion

In terms of physics, setting means the formation of a thixotropic reversible coagulation structure that strengthens in time. Strengthening occurs due to an increase in the number of colloidal-sized particles of the solid phase per unit volume. Setting is caused by water binding by the surface of cement grains and new formations. The formation of these new structures is an independent process that precedes and significantly affects water-cement paste hardening (Kapranov, 1976; Rebinder, 1966, 1968).

As a result of setting, intense water binding occurs, and, as a consequence, permittivity decreases due to water structuring in new high-dispersion hydrated phases. When introduced, $AlCl_3$, $Al_2(SO4)_3$, $FeCl_3$, $Fe_2(SO4)_3$ shorten the setting time but do not result in an instantaneous setting. It means that setting depends not only on Al+3 impact but also on intense water binding (Akhverdov, 1981).

The aggregative stability of a dispersion system largely depends on the composition of the dispersion medium and can be altered through the introduction of electrolytes. For lyophilic systems, electrolyte introduction increases the coagulation rate, and, when a certain (critical) electrolyte concentration is reached, the coagulation rate reaches its limit.

A charged surface (a statistical value) represents alternating areas with positive and negative charges (with one type of charge dominating, which predetermines the overall charge of the surface). Therefore, when the surface of cement grains is

multivalent ions into the adsorption layer, and their impact on the electrical double layer (EDL) are possible. The sign of the potential-determining ion layer charge and the value of the diffusion layer characteristic in cement dispersions are largely related to the ion composition of the dispersion medium. During hydration, the potential value and charge sign change.

The ion composition of the dispersion medium changes as a result of phase transformations in the system as well as the impact of fields and electrolytes. Be-

sides, it can be done with the introduction of poorly soluble substances whose ions, due to adsorption, affect the composition of the potential-determining layer of the dispersion phase.

The pH value of the medium significantly affects the ζ-potential (zeta potential is the difference between the potentials of the dispersion medium and stationary fluid layer surrounding the particle) since H+ and OH- are easily adsorbed due to their small size and dipole moment. In a cement system, pH grows, which can also result in changes in the ζ-potential and possible charge exchange.

Coagulation processes play an important role in the formation of cement stone due to the discharge of particles, reduction of their potential, and compression of the diffusion portion of the electrical double layer (Svatovskaya and Sychev, 1983).

By reducing the potential of the adsorption layer or compressing the diffusion portion of the electrical double layer (or the interparticle distance), it becomes possible to control the setting time or initial density of grains in stone. Reduced permittivity decreases the thickness of the diffusion layer. Therefore, water binding decreases the thickness of water films, within which the EDL thickness is reduced, i.e., setting becomes less hindered. The hydration process leads up to setting, which is based not only on chemical water binding (an increase in the solid/liquid (S/L) ratio) but also on liquid permittivity reduction.

The introduction of "active" ions affects the potential of the adsorption layer and, therefore, the EDL characteristics, the structuring degree of boundary water layers, and transport of active particles, i.e., colloidal chemical and condensation phenomena. Besides, through their charge state and the nature of the chemical environment (Judina, 2019; Judina and Verstov, 2013), active ions affect the activity of the centers. The electrolyte ions with a charge opposite to that of the particle surface produce the coagulation effect. The higher the valence and the larger the radius, the more intense the effect. A reduction of the zeta potential to approx. 30 mV leads to coagulation.

With trivalent ions introduced, e.g., Al^{+3}, the capacity arises to reduce the zeta potential more intensely in comparison to monovalent ions, which is important: their appearance in the setting process at ion hydration.

Being highly active, multivalent ions demonstrate a strong adsorption capacity in relation to the solid phase, they more easily (in comparison to other ions) penetrate the electrical double layer of the ions with the opposite charge and replace there the potential-determining ions, thus changing the charge of the solid phase surface.

Possible activation methods considered at the level of colloidal chemical phenomena are summarized and given in Fig. 1.

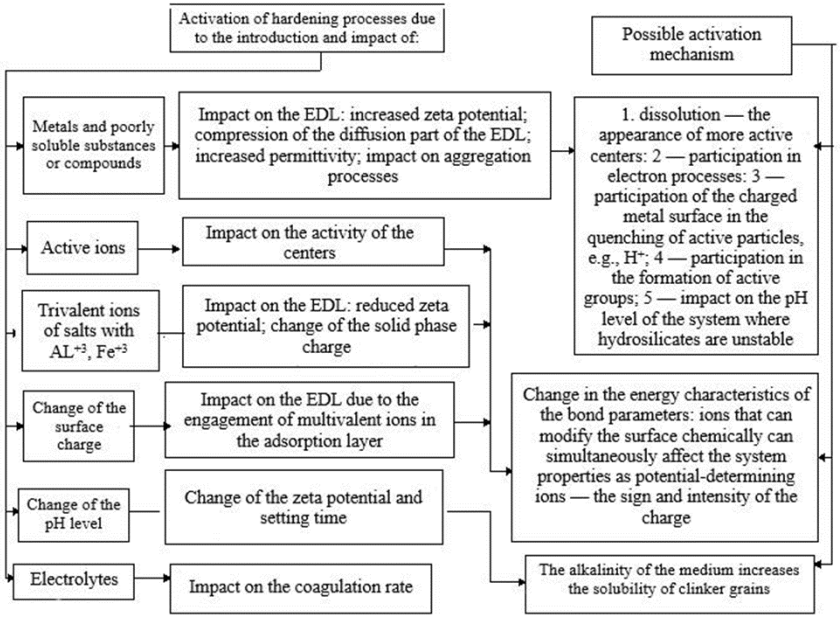

Figure 1. *Diagram of possible hardening activation methods at the level of colloidal chemical phenomena*

To reduce energy consumption during thermal activation (steam curing) of concrete hardening, it is necessary to ensure acceleration of hydration and strength gain at an early stage. The strength of cement stone depends on its porosity, hydration degree, and energy characteristics of the bonds.

$$= f(p, \alpha, E_b),$$

where p — stone porosity, α — the hydration degree, E_b — the energy characteristics of the bonds formed by the cement phases.

The cement stone strength increases with the speed exceeding the directly proportional hydration degree of the binder and is characterized by the quantity and quality of bound water. Water filling the pores and cavities of the binder represents a solution with a complex physical and chemical composition that interacts with solid particles and is, to a certain extent, a bound solution. The kinetics of chemical water binding predetermines the structure of new cement stone formations, which develops during setting.

The dependence of the concrete strength on the water/cement ratio is associated with the cement stone structure formation process. When the water/cement ratio

increases (water surplus), the hydration process slows down, and concrete porosity increases, which has an adverse effect on strength. Low porosity of cement stone is ensured by a decrease in the water/cement ratio.

A decrease in the water/cement ratio accelerates crystal formation in cement stone, is accompanied by qualitative changes in its structure, and increases the concentration of alkalis in the liquid phase (Rebinder, 1968), thus boosting the hydrosilicate formation process.

The interaction between cement particles and water with ions of some chemically active compounds can significantly accelerate the induction period — the cement gel setting time and the formation of crystal hydrate complexes causing its transformation and passage into a stone -like state, which affects the kinetics of cement stone strength gain.

Extremely small concentrations of ions capable of compressing the double layer due to the action of counterions are necessary for impact on the electrical double layer. The introduction of foreign ions into the hydrosilicate structure leads to changes in the energy characteristics of the bond, which affects the plasticity of the mix and cement stone strength (Svatovskaya and Sychev, 1983).

The pH level of the medium plays an important role in hydrate formation (hardening). The alkalinity of the medium intensifies the hydration of clinker grains and the pH level of the liquid phase, thereby increasing their solubility (Grushko et al., 1983) since OH- radicals have a smaller size in comparison to water molecules and penetrate the pores of the new formations' shield film more freely. The acceleration of the hydration of silicate phases is ensured through an increase in the concentration and intensity of active centers on the surface of cement minerals as well as through the introduction of ions participating in the formation of the binding system into dispersion.

The activity of the binding system can be controlled by means of not only chemical modification of the surface but also surface electron processes due to changes in the concentration of free charge carriers in the surface vicinity, e.g., through exposure to an electric field (Bertolini et al., 2009; Zhang et al., 2006).

Ions that can modify the surface chemically can simultaneously affect the system properties as potential-determining ions.

The ion composition of the liquid phase affects the intensity of active centers, colloidal chemical properties of dispersion, morphology of cement phases, properties of cement phases. Ion exchange makes it possible to affect the defectiveness degree of surface atoms and the activity of adsorption centers as well as the colloidal chemical properties of the surface (the sign and intensity of the charge).

The surface/liquid interaction, in terms of electrostatic forces that manifest in bonds of atoms or ions of the surface and structure of the liquid in boundary

and free layers, affects the consistency of the mix. The introduced substances, depending on their nature, chemically modify the surface of minerals in such a way that the activity of the surface in reactions with water disappears or noticeably increases. Such changes in the ion composition of the surface also have an effect on its charge and the whole gamma as well as colloidal chemical phenomena that manifest at the phase boundary, on the one hand, and mobility (stiffness) of the whole heterogeneous system, on the other hand.

Conclusion

As a result of the performed generalizations and the analysis of studies addressing the hardening of binding systems and its implementation in construction at the level of colloidal chemical phenomena, and the energy of interaction between the binder and water in construction mix preparation, we have determined the main directions of boosting the processes in binding systems through various types of energy impacts.

To ensure hardening activation, the following is required:

– impact on the composition of the potential-determining layer of the dispersion phase;

– an increase in the pH level, which results in changes in the zeta potential and possible charge exchange;

– a decrease in the interparticle distance or reduction of the diffusion portion of the electrical double layer.

The introduction of active multivalent ions contributes to the reduction of the zeta potential. Besides, they can become potential-determining ions in the system. They affect the intensity of active centers, colloidal chemical properties of dispersion, morphology and properties of cement phases.

The introduction of foreign ions into the hydrosilicate structure leads to changes in the energy characteristics of the bond, which affects the plasticity of the mix and cement stone strength.

Studies on phenomena that occur during binding system hardening activation as well as the implementation of the mechanism of these phenomena will make it possible to apply various methods of construction mix components (cement, mixing water, fillers) activation during preparation more widely in order to improve the physical and mechanical, processing, and performance properties of mixes.

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ANALYSIS OF THE STUDY OF MICROBIOLOGICAL INDICATORS OF BROILER CHICKEN MEAT PROCESSED ON THE ILU-10 ELECTRONIC ACCELERATOR

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Abstract. *The article presents studies on the processing of meat of broiler chickens using the ILU-10 electronic accelerator for various periods of storage: up to 14 days - chilled meat and up to 4.5 months - frozen. The recommended dose of radiation is 2-8 kGy, which increases the period shelf life at +2°C for approximately 14 days.*

Analysis of the revealed manifestations of microbiological contamination, identified types of various signs, incl. salmonella for 10 and 11 CFU / unit.

The present study showed that the scores for the control group were relatively low compared to other studies.

It was found that the frequency of events as low as 2 - 8 kGy led to the frequency of microbes. It is indicated that there were no observations of colony forming units in samples irradiated at 8 kGy.

Keywords*: radiation treatment, poultry meat, microbiological contamination.*

Currently, the Republic of Kazakhstan imports a significant amount of meat and meat products. Despite the priority state support for livestock and poultry farming by the state, Kazakhstan remains import dependent on meat and meat products. The main volume of imports fell on poultry meat - 168.5 thousand tons for $167.3 million tenge (https://eldala.kz/) from the countries of the European Union, the USA, Argentina, Brazil. Poultry farming is the most dynamic branch

of agriculture in the Republic of Kazakhstan, the share of poultry meat production is 65% of the total production [1].

According to the safety requirements for poultry meat and products of its processing, established by the Technical Regulations of the Customs Union "On Food Safety" (TR CU 021/2011), one of the priority areas of state regulation in the field of food safety is the further development and strengthening of the quality control and supervision system and safety of food raw materials and foodstuffs.

In poultry farming, one of the main tasks is to ensure the quality and safety of raw materials by the effective processing and protection of poultry from microbiological and infectious diseases. The development of the food industry along with the production of food products raises the problem of its long-term storage.

The utility and practicality of food irradiation has been exploited for more than three decades after extensive research and development on its technological aspects. Electromagnetic food processing is now recognized as an efficient and safe process. Today, nearly 50 different products are irradiated in more than 25 countries. Today, electromagnetic food processing is a promising food safety technology to improve hygiene and increase shelf life and distribution. Ionizing radiation is used to convey beneficial changes in foods and has been recommended as a method for ensuring the safety of meat products [2,3,4].

The usefulness and acceptability of irradiated foods have been evaluated by various expert committees such as the Joint Experts Committee on Food Irradiation (JECFI), the International Atomic Energy Agency (IAEA), the World Health Organization (WHO), and the Food and Agriculture Organization (FAO), and after considering all the data, it was recommended that radiation exposure of food to any food in a total average dose up to 10 kGy does not pose a toxicological hazard, nor does it cause nutritional or microbiological problems. Radiation doses in excess of 10 kGy can lead to food sterilization, as is the case with meat products prepared for NASA's spaceflight program. Irradiation (1 kGy - 10 kGy) is a successful method for reducing the microbial load of food. Irradiation increases the shelf life of meat, chicken, and fish products by reducing the number of spoilage microorganisms, and, as with heat treatment, this process can also inactivate enzymes that would otherwise contribute to meat spoilage. It also reduces the microbial load on foods such as spices and meat products.

The radiation resistance of organisms that cause food poisoning is commonly associated with poultry, so the choice of the recommended dose has been determined and taken into account [2,3,4].

In this study, a microbiological assessment was made of the effect of UV treatment and radiation treatment of birds during housing, storage on shelf life extension.

The objects were broiler chickens aged from 4 to 8 weeks, which were obtained from a local producer of poultry meat taken immediately after slaughter at a poultry farm.

The carcasses were cut into eight parts: two legs, two wings, two parts of the back and two parts of the breast. These pieces were then individually loosely packaged in new plastic bags. Packaged samples sent to the storage room temperature (4°C) transported to the installation for processing. Meat samples before processing were packaged and prepared for sale in plastic bags and trays. The broiler breast fillets were packaged four fillets per polystyrene tray and wrapped with plastic wrap in shrink wrap.

The meat of broiler chickens was processed by radiation treatment on an electronic accelerator - ILU-10 from 2 to 10 kGy in RSE "Institute of Nuclear Physics"

Initially, an untreated piece from the entire batch was used to determine initial microbial counts, but later experiments analyzed a piece from each bird after treatment.

The experiments were carried out in triplicate with each radiation group consisting of 10 samples; four breasts in a tray constituted one sample.

After the samples were transported from the installation for radiation of poultry meat samples with a charged electron beam or bremsstrahlung at the ILU-10 accelerator with doses up to 10 kGy, they were kept at a temperature of 4°C to ensure that the samples were at the same temperature for testing . Breast fillet, fillets have been tested for microbial content. Each exposure group consisted of 10 samples, with four breasts per tray making up one sample.

Microbiological parameters were determined in samples of white and red meat of chickens after irradiation on an electronic accelerator with doses of 2-8 kGy and 3 months of storage at a temperature of -18°C (Tables 1 and 2). Microscopic examination of imprint smears from the deep layers of the femoral and pectoral muscles after slaughter in the meat of the control group, the value of QMAFAnM averaged 1.9-2.0 x102 CFU /g, and when irradiated with a dose of 8 kGy, this indicator decreased to 5.7-5.5x102 CFU/g, respectively.

Table 1

Microbiological indicators of meat of broiler chickens after processing by various types and storage at a temperature from 0°C to +2°C

Name of defined indicators	**Hygienic standard**	**Test results**	
		on an electronic accelerator	
		2 kGy	**8 kGy**
After slaughtering			
QMAFAnM	not more than $1,0x10^4$ CFU/g	1,9-2,0 $x10^2$ CFU/g	5,7-5,5$x10^2$ CFU/g
Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Less than 10 CFU/g	Less than 10 CFU/g
5 days			
QMAFAnM	not more than $1,0x10^4$ CFU/g	4,2-5,2 $x10^2$ CFU/g	6,8-7,2$x10^2$ CFU/g
Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Менее 10 CFU/g	Менее 10 CFU/g
14 days			
QMAFAnM	not more than $1,0x10^4$ CFU/g	4,5-5,5$x10^3$ КОЕ/g	7,7-8,2 $x10^3$ CFU/g
Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Менее 10 CFU/g	Менее 10 CFU/g

After 5 days, the QMAFAnM indicator in the meat of the control group increased by 2.2 times, and after 14 days it averaged 1.1-2.6x10^4 CFU/g, which exceeded the value of hygienic standards by 2 times.

Treatment with ILU-10 at 2–8 kGy reduced the number of coliforms, E. coli, aerobic bacteria and psychrotrophs on the microbiological parameters of poultry meat at a temperature of -18°C compared with the control group that did not receive irradiation (Table 2).

Table 2

Microbiological indicators of meat of broiler chickens after processing by various types and storage at a temperature of -18°C

Name of defined indicators	**Hygienic standard**	**Test results**	
		on an electronic accelerator	
		2 kGy	**8 kGy**
45 days			
QMAFAnM	not more than 1,0x10^4 CFU/g	1,3-1,6 x10^2 CFU/g	4,5-4,8 x10^1 CFU/g
Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Less than 10 CFU/g	Less than 10 CFU/g
90 days			
QMAFAnM	not more than 1,0x10^4 CFU/g	2,2-5,5 x10^2 CFU/g	5,6-7,6x10^2 CFU/g
Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Less than 10 CFU/g	Less than 10 CFU/g
135 days			
QMAFAnM	not more than 1,0x10^4 CFU/g	2,5-3,1 x10^2 CFU/g	5,4-6,5 x10^1 CFU/g

Coliforms bacteria (coliforms)	not allowed in 0,1; 0,01 g	Not detected	Not detected
Pathogenic, in including salmonella	not allowed in 25,0 g	Not detected	Not detected
L. monocytogenes	not allowed in в 25 g	Not detected	Not detected
Mold	Not more than 10 CFU/g	Less than 10 CFU/g	Less than 10 CFU/g

The radiation dose of ILU-10 with rays of only 2 kGy leads to a decrease in the total number of aerobic organisms by 2-3 times. A radiation dose of 8 kGy is effective in reducing the number of enterobacteria, as well as coliform and total mesophilic bacteria in spices.

It can also be seen from the table that treatment on an electron accelerator with doses from 2-8 kGy leads to a decrease in microorganisms. Cases of isolation of bacteria of the genus Salmonella, L. Monocytogenes, coliform bacteria (bacteria of the Escherichia coli group) were not found.

Thus, the studies have shown that the meat of broiler chickens treated with ILU-10 for various periods of storage: up to 14 days - chilled meat and up to 4.5 months - in frozen form meets the requirements of SanPiN 2.3.2.1078-01, which gives reason to use it for food purposes without restriction.

Based on the results of the experiment, it is possible to estimate the likelihood of re-infection of the bird with either Salmonella, or Staphylococcus, or both. The recommended dose of radiation is 2-8 kGy, which increases the shelf life at +2°C by about 14 days. This treatment also led to a decrease in the number of viable species of various microorganisms, incl. salmonella for 10 and 11 CFU / unit.

The present study showed that the scores for the control group were relatively low compared to other studies. The relatively low scores were due to the fact that boneless and skinless breast fillets such as those used in the study are expected to have a low microbial load because the fillets have no skin to which bacteria can attach. It is believed that parts of a chicken, such as thighs, that have skin will have a higher microbial load because the bacteria mostly attach to the skin.

Radiation doses as low as 2–8 kGy led to a decrease in microbes. It is indicated that no viable colony forming units were found in samples irradiated at 8 kGy.

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PROBLEMS OF FUNCTIONING AND CONTROL OF EXISTING SYSTEMS OF SHELTER OF EMPLOYEES OF ENTERPRISES AND THE POPULATION FROM MAN-MADE AND MILITARY EMERGENCIES, PROMISING WAYS OF MONITORING THEM

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Abstract. *The article provides an overview of the problems of controlling the existing systems of shelter of the population from man-made and military emergencies, the construction and algorithmization of promising protection systems based on the domestic element system at civil defense protection facilities (shelters and protective structures), with the possibility of controlling the phased modernization of existing facilities protection facilities. In general, the article is devoted to the possibilities of using remote means of information transmission (signals generated by teams of detectors and video monitoring) as a tool for early*

detection of malfunctions and signs of fire occurrence for making operational management decisions when directing the actions of the maintenance and monitoring group.

Keywords: *Civil defense, protective structures and shelters, video monitoring, alarm system, retransmission of signals to higher levels of management.*

The analysis of emergencies that occurred at facilities located on the territory of large cities, near highways, indicates that probable emergencies, the damaging factors of which can affect buildings and personnel located in it, are the following:

1. Causing damage to buildings of varying severity and hitting visitors and staff with excessive pressure in the front an air shock wave formed because of various explosions:

• Fuel-air mixture in case of a motor vehicle accident (terrorist attack) with the destruction of fuel tanks of cars.

• As a result of terrorist acts near structures accompanied by the explosion of condensed explosives.

2. Defeat of visitors, staff, and destruction of material assets because of fire.

3. Termination of life support of buildings.

4. The emergence of riots, the manifestation of extremism

5. In case of a sabotage act, visitors and staff may be affected due to damage from an emergency chemically dangerous substance, with radioactive contamination of the area, bacteriological infection and infectious diseases (primarily very gastrointestinal diseases):

• Chemical damage to visitors and staff as a result of chemical accidents: (occurred at hazardous production facilities located on the territory of the city and accompanied by the release (spill) of an emergency chemically hazardous substance; occurred as a result of motor vehicle accidents on highways with a spill of an emergency chemically hazardous substance; occurred as a result of transport accidents on the railway with a spill of an emergency chemically hazardous substance).

• Radioactive contamination of the area.

• Use of mercury.

• Spread of infectious diseases.

Shelters, shelters and other protective structures are an integral part of the civil defense system. The system is quite complex and saturated with a large number of life support systems (electricity, communications, drinking and technical water, sewerage, air conditioning and conditioning system, which means that it is expensive and difficult to operate. Further development of protective structures systems should ensure not only the autonomy of its functioning, but also the possibility of choosing an algorithm for connecting (enabling) other elements

of automated systems, as well as working together with control and life support systems of the protected object and the possibility of timely signal transmission to higher-level management of the Ministry of Emergency Situations [1-5], but despite the publication of federal laws, the functioning of protective structures are extremely vulnerable to the human factor:

- The competence of the owner's representative (who, according to their official duties, coordinate activities for the maintenance of protective structures, maintenance and compliance with the necessary standards);
- Qualification of officials (authorized in the field of civil defense) and lack of specific standardization;
- Difficulty of control for supervisory authorities (if the protective structure is located on the territory of a defense enterprise, at least the second form of admission is required, and these are only regional departments), a large distance;
- Financing on the residual principle in the conditions of the economic crisis and the construction of a market economy, the RF PR 227 on Reimbursement of Expenses for the Preparation and Conduct of Civil Defense Measures does not actually work and depends on local budget funds, the mechanism of repayment through the federal Treasury is extremely difficult.
- Dilapidation of the existing fund;
- False reports on the existing equipment and readiness of protective structures.

Currently, the problem of limited resources, import substitution, modernization (many systems and other elements of automated control systems of Protective structures that are more than 20 years old), timely quality maintenance (maintenance), rapid troubleshooting and monitoring of life support systems is very urgent.

- there is no possibility of implementing monitoring control by the Department of Supervisory Activities and Preventive Work (OND, etc.) of the Ministry of Emergency Situations on the problems listed above.

As a solution to the above-mentioned problems and within the framework of the state program of import substitution conducted by the Government of the Russian Federation for the construction of a subsystem for the control of a promising automated control system of Protective structures, the following systems are proposed protection controls built on elements (adjustable sensitivity threshold, for heat, light, air and liquid flow, signal transmission by remote means).

The ability to monitor (remotely) and transmit information via a GSM module or Ethernet technology will significantly reduce the response time and material costs for timely troubleshooting maintenance, as well as operational monitoring of the operability of life support systems. The GSM module is proposed to be implemented on the basis of existing software: M2M24 Cloud TCP connection server - cloud software for connecting via GPRS (TCP/IP) nodes of dispatching

systems operating in the "Client" mode: dispatching programs and TELEOFIS equipment (modems, terminals, routers, etc.) connected to the metering devices. The server allows you to administer many devices and supports the operation of several communication channels [5].

In order to solve the problems, the following algorithm is proposed for the operation of a promising object control system (Fig. 1).

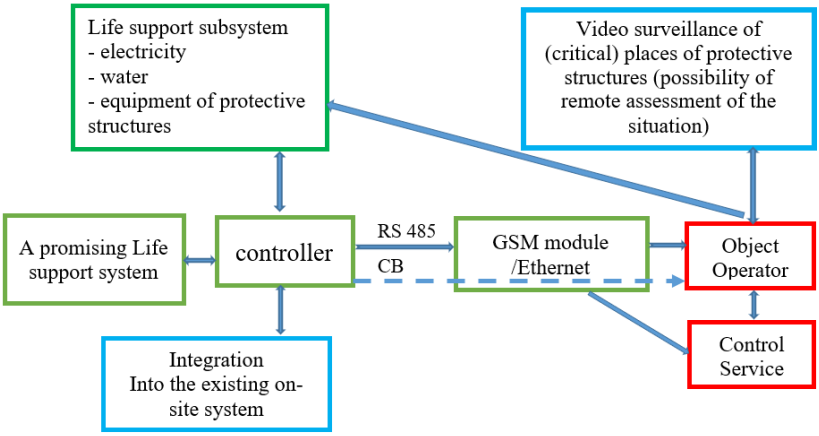

Figure 1. *The sequence of functioning of the object's life support system*

To detect a malfunction, a signal is transmitted from the sensors of illumination, flow, radiation level or chemical contamination, depending on the specifics of the industrial zone, from the points where the equipment is located to the controller, where the electronic module is used to measure, analyze and calculate parameters based on the current and previous values of the following factors:

- Water and sewer flow sensor;
- Light level;
- The temperature of the medium inside the structure of its increase;
- Air flow velocity and filter contamination level;
- Sensors of radioactive and chemical contamination;
- wind speeds.

When processing a set of factors and obtaining a probabilistic estimate, the controller records the state level of life support systems and transmits notifications to external circuits [1]. During operation, the controller constantly monitors the state of the system. If the values deviate from the norm, a notification "Need for maintenance" is generated, the "Malfunction" indicator is turned on, a signal is transmitted to external circuits via the RS-485 interface or via an alarm loop

(SHS). In case of malfunction of the controller, a "Malfunction" notification will be generated with a status indication and notification transmission to external circuits [4]. In case of an open or short circuit, the controller switches to the "Malfunction" mode, which means this function allows for integrity monitoring without additional devices [2].

The possibility of integration into the life support system of video surveillance protective structures of critical or potentially dangerous places, without the direct introduction of video surveillance cameras into the protection system, will avoid an excessive increase in the flow of information, reduce the number of personnel on duty and significantly increase the objectivity of monitoring large spaces or dangerous places, as well as make a correct assessment of the current situation. Remote transmission of information to the control service will allow:

- if necessary (the specifics of production or the small size of the object) to carry out remote monitoring of the SDR of the object;
- reduce the time of troubleshooting or malfunction of the SDR;
- organize operational interaction of the service with the operator or representative of the facility, and, if necessary, with the dispatcher of the fire service.

The considered algorithm for constructing a protective structures control system makes it possible to optimally build not only a modern monitoring system, but also to gradually modernize existing systems in accordance with emerging needs and capabilities. The use of modern and reasonably reliable GSM and Ethernet technologies for data flow transmission will significantly increase the speed of operational management decisions. Remote analytics is a new vector of development of the direction to increase the level of readiness not only for supervisory authorities, but also for the development of uniform standards depending on potential threats and economic opportunities.

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EXPANSION OF METAGALAXY FROM THE POINT OF VIEW OF RELATIVISTIC KINEMATICS

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Annotation. *The article highlights some issues of relativistic kinematics (or Einstein's special theory of relativity – SRT). Formulas approximating transformations of spatial coordinates and time during the transition from an inertial reference system (IRS) to a non-inertial system moving relative to IRS with constant acceleration are given. In the light of the proposed additions to classical relativistic kinematics, the expansion of the observable part of the Universe – Metagalaxy - is considered. The age and size of the Metagalaxy are clarified, it is shown that there is no need to accept the hypothesis of the existence of dark energy to explain this phenomenon.*

Keywords: *relativity theory, acceleration of reference systemy, expansion of Metagalaxy, dark energy.*

1. Introduction.

Relativistic kinematics is one of the most important components of modern physics. In fact, it is a physical theory of philosophical categories – space and time, which strictly proves the inextricable connection of the mentioned categories, the impossibility of overcoming the "light barrier" $c = const$ and many other [1]. The conclusions of relativistic kinematics (more precisely, the kinematics of objects moving at very high speeds) go far beyond the "everyday" experience, and therefore they seem paradoxical. One of them – the statement about the slowing down of the passage of time in a moving inertial reference system – generally looks implausible. However, this conclusion, like all other provisions of IRS, is the result of unerring mathematical transformations of the initial equations; it is experimentally confirmed, for example, by the results of measurement by a motionless observer of the lifetime of unstable elementary particles accelerated in the CERN ring accelerator to a speed approaching *c* [2].

In SRT, two inertial reference systems are studied, the first of which, having spatio-temporal characteristics x, y, z, t , is motionless, and the second with

characteristics x, y, z, t at $t > 0$ is moving away from the first with a constant velocity v_0 that can tend to c. The systems coincide at $t = t = 0$, then the reference system II moves so that the equally directed x axes and x continue to remain on the same straight line, and the other two pairs of axes maintain parallelism. Under the described conditions, the simple rule of addition of velocities of Galileo-Newton kinematics, corresponding to "everyday" experience, is not fulfilled [1]. In the general case

$$\frac{dx}{dt} = \left(\frac{d\xi}{d\tau} + v_0 \right) \Bigg/ \left(1 + \frac{d\xi}{d\tau} \frac{v_0}{c^2} \right), \qquad (1)$$

that is, an experimenter who, while in system I, measures the speed of an object moving at a speed $\frac{dx}{dt}$ in system II, receives its value $\frac{dx}{dt} < \frac{d\xi}{d\tau} + v_0 < c$. Equality (1) is a mathematical record of one of the postulates of the special theory of relativity formulated by A. Einstein: the speed of electromagnetic waves is not affected by the movement of emitters and receivers relative to each other, c is a world constant.

The inertial reference systems considered in the classical SRT are "mirror-like" indistinguishable: the second of them is also moving away from the first with a constant velocity ($-v_0$), in both systems the laws of Newton's mechanics are fulfilled. However, the indistinguishability of the studied systems disappears if one of them, for example, the second, begins to move with acceleration. In an accelerated moving system, inertia forces are detected – it becomes non-inertial. Transformations of spatial coordinates and time during the transition from a motionless inertial system I to a non-inertial system II are not described by the well-known SRT formulas, in this part relativistic kinematics requires clarification. The purpose of this work is to formulate them. When achieving this purpose, there was no need to go beyond the "school" mathematical analysis [3]. The obtained calculation formulas were used to describe the motion of galaxies, that is, massive substance objects moving in cosmos space, as astronomical observations showed, at very high speeds [4].

2. Results and their discussion.

Let's assume that at the initial moment of time in the center of the reference system I x, y, z, t there is a real object (a material point – MP). The center of system II x, y, z, t, which coincides with the center of the first system, is rigidly connected to MP. At this moment, the object begins to move along the x-axis with acceleration a. Together with it, the second system comes into accelerated motion without rotating.

The MP in system II remains motionless during the entire observation time, so that $\zeta = \eta = \zeta = 0, \frac{d\xi}{dt} = 0$. If the reference systems were moving away from each other at a constant speed, then, as follows from equality (1), an observer located in the center of a motionless system would have recorded the coincidence of the velocities of MP v_0 and system II $\frac{dx}{dt}$. It is reasonable to assume that in a more complex situation $\frac{dx}{dt} = v(t)$. The MP in system II remains motionless during the entire observation time, so that $\zeta = \eta = \zeta = 0, \frac{d\xi}{dt} = 0$. If the reference systems were moving away from each other at a constant speed, then, as follows from equality (1), an observer located in the center of a motionless system would have recorded the coincidence of the velocities of MP v_0 and system II $\frac{dx}{dt}$. It is reasonable to assume that in a more complex situation $\frac{dx}{dt} = v(t)$. Let's take into account the existence of an insurmountable "light barrier", due to which the increase in the speed of the observed MP (and system II) should stop over time. Note that to interpret this phenomenon, it is not necessary to invent braking forces – this effect is easily explained within the framework of relativistic kinematics by the properties of space-time.

It is proposed not to establish the exact type of dependence v , but to approximate it with a function that tends to *at*, if $t \to 0$, and whose slope to the abscissa axis decreases monotonically to zero, if $t \to \infty$,

$$v(t) = \frac{dx}{dt} = c\left[1 - \exp\left(-at/c\right)\right]. \qquad (2)$$

Integrating equality (2) in the range 0 – *t*, we obtain the time dependence *x*:

$$x = \int_0^t v(t)dt = ct + \frac{c^2}{a}\exp\left(-at/c\right) - c^2/a \quad (3)$$

It follows from formula (3) that,

- when $t \to 0$, the path length of an object gaining speed is proportional to the square of the observation time (as in kinematics of MP, $x = at2/2$);
- if $t \to \infty$, the motionless observer must fix the approximate proportionality of the values of *x* and *t* ($x \approx ct - c2 / a$).

Suppose the object and non-IRS II first accelerated away from system I, reached a velocity $\vec{v}_0$, at $t = 0$ began to approach the motionless observer with acceleration ($-\vec{a}$) and move away from the "light barrier"; so at the time before stopping, their velocity modulus decreased according to a linear law:

$$v(t) = \frac{dx}{dt} = v_0 - at\,. \qquad (4)$$

As is known, the results of measuring time intervals Δt and $\Delta t'$ do not coincide if the experimenters are in two IRS, which are moving away from each other at a speed $\vec{v}_0 = const$ [1]. In this case, there is a "twins paradox":

$$\Delta t' < \Delta t; \quad \Delta t' = \Delta t\sqrt{1 - v_0^2/c^2}\,. \qquad (5)$$

In the situation discussed here, system II is non-inertial. Hence, the ratio between the values Δt and $\Delta t'$ should be calculated using the integral formulas given below, which are obtained after replacing v_0 in equality (5) with functions v (2) and (4):

$$\Delta\tau = \int_0^{\Delta t}\left[1 - (e^{-at/c})^2\right]^{1/2} dt\,, \qquad (6)$$

$$\Delta\tau = \int_0^{\Delta t}\left[1 - \left(\frac{v_0 - at}{c}\right)^2\right]^{1/2} dt\,. \qquad (7)$$

It follows from equations (5), (6) and (7) that in any reference system moving uniformly or constant accelerated, the flow of time slows down regardless of the direction of the vectors $\vec{v}$ and $\vec{a}$.

Let us now determine the kinematic characteristics of the Metagalactic elements moving away from the Milky Way.

It is established that the total number of detected galaxies, quasars and other cosmic macro objects is approximately 10^{11} -10^{12}. With rare exceptions, these objects are moving away from the terrestrial observer, and Hubble's law is fulfilled (although not strictly), according to which their velocity v is proportional to the distance R to "our" galaxy [5]:

$$v = HR, \qquad (8)$$

where $H \approx 22 \cdot 10^{-19}$ c^{-1} is a constant. Extrapolation of the experimental data obtained by E. Hubble into the distant past leads to the hypothesis of the Big Bang (BB), from which the age of Metagalaxy should be counted. At present, the existents of the Big Bang is beyond doubt; within the framework of modern cosmology, this event is considered as an axiom of the standard model of the birth and transformation of the observable part of the Universe [4].

It is assumed that the current moment separates $1/H \approx 4{,}5 \cdot 10^{17}$ s (~14 billion years) from BB. Approximately $5 \cdot 10^{16}$ s after BB, that is, in the epoch of matter reionization, a set of Metagalactic elements was formed [6], which then evolved in accordance with the laws of SRT. Thus, during most of the existence of Metagalaxy (about 90%), the movement of its large-scale elements should be described by the equations of relativistic kinematics proposed in this message.

It should be noted that Hubble's law is of great importance for the formation of modern cosmology as a science, since the generally accepted ideas about the appearance of superdense and superheated matter in BB began to form precisely after the fact of the scattering of metagalactic elements was established. Nevertheless, the regularity corresponding to formula (8) can by no means be considered accurate and strictly justified for the following reasons:

1) There are a small number of galaxies that are approaching the terrestrial observer, and not moving away from it. These include, for example, the nearest neighbor of the Milky Way – the Andromeda nebula.

2) There is no reason to believe that the velocities of all galaxies and quasars equidistant from the Milky Way are the same or close. This assumption is clearly refuted by the results of measuring the quantities v and R, which form a cloud of points in the "space" $v - R$, the width of which reaches 10^6 m/s [5].

3) The validity of Hubble's law has been postulated for space objects that are "only" $R \sim 10^{23}$ m away from the Milky Way, while the farthest of the discovered galaxies is located at a distance of about a thousand times greater from the terrestrial observer. The comparison of the above numbers raises serious doubts that this law applies to the entire Metagalaxy at all times.

4) It is impossible to agree with the opinion about the validity of equation (8) for all star clusters observed at a certain moment in time, since information about their velocities comes to the observer with a time delay, the value of which varies significantly with R (at $R \sim 10^{23}$ m it is equal to 10^6 years, and at $R \sim 10^{26}$ m the delay by the time is approximately 10^{10} years).

5) The experimental data presented in the "space" $v - R$ by a set of widely scattered points relate to various cosmos objects characterized by mismatched initial velocities and different equations of motion $R = f(t)$.

6) If the path x traversed by the object under study and the velocity of this object $\frac{dx}{dt}$ are related by equation (8), then both of these values increase with time equally infinitely ❙❙ exponentially. However, the speed of any object in accordance with the fundamental provisions of the special theory of relativity cannot exceed the speed of propagation of electromagnetic radiation in a vacuum. Thus, equation (8) is just an imperfect approximation of the real dependence $v = f(R)$.

Proceeding from the above, we consider the movement of the elements of Metagalaxy, taking into account formulas (2) and (3), which approximate the time dependencies v (t). and x (t) when changing the argument in an infinitely wide interval, $0 < t < \infty$.

These formulas are reduced to the form

$$at = -c \ln(1 - v/c), \quad (9)$$

$$aR = cat - cv. \quad (10)$$

Obviously, if an object is detected at a distance R from the Milky Way, which is located in the center of a non-inertial system of reference and has a velocity v, then equations (9) and (10) must be used to calculate unknown values of the acceleration modulus of this object a and the time of its movement in space t.

The experimental data are as follows: at R approximately 3×10^{22} m, the velocity of the scattering of galaxies is about 0.8×10^6 m/s; at twice the distance R, the galactic star clusters located there move at a speed of $\sim 1.2 \times 10^6$ m/s [5]. Calculations performed on the basis of the cited data lead to the conclusion that

- the acceleration of the scattering galaxies is negligible, it is equal to (1,1-1,2) $\times 10^{-11}$ m/s^2;
- these elements of Metagalaxy move uniformly (or almost uniformly);
- so, they are affected by negligible forces, the nature of which is not discussed in kinematics.

Suppose that the galaxies discovered in recent years, which are the furthest from the terrestrial observer and have a near-light velocity (0.98 c), are sent to the boundaries of the observable Universe immediately after the Big Bang with the same acceleration as space objects more close to Earth, whose velocity $v << c$. Then it follows from equations (9) and (10) that such high-speed objects reached the boundaries of the Metagalaxy in $\sim 9.8 \times 10^{19}$ s, moving away from the Milky Way by $\sim 22 \times 10^{22}$ m during this time.

In cosmology, it is customary to estimate the age of the Metagalaxy and its size based on Hubble's law – by the values of "Hubble time" $1/H \approx 4{,}5 \cdot 10^{17}$ s and "Hubble distance" $c/H \approx 13{,}5 \cdot 10^{25}$ m [4]. However, a critical analysis of the mentioned law (see above) suggests that these estimates cannot be considered reliable. The characteristics of Metagalaxy given in this article are more realistic; it follows from them that the age and size of the observable Universe are underestimated by" Hubble calculations" by 220 and 160 times, respectively.

An alternative statement to the concept presented here is that galactic "express trains" far from the Milky Way move with a large positive acceleration due to negative pressure (antigravity) [7]. It was proposed to consider the source of antigravity as a "certain substance" – not detected experimentally (?)dark energy, which supposedly fills the Universe evenly, accounts for about 70% of its total energy-mass and provides accelerated scattering of galaxies according to Hubble's law.

The hypothesis of the existence of dark energy has many authoritative supporters who consider it one of the consequences of the general theory of relativity (GRT). And yet, there are many reasons to criticize such ideas about "everything that exists":

1) The author of the GRT, A. Einstein, introduced the cosmological constant into the GRT equations, accepting as true the idea of the stationarity of the Universe, refuted by astronomical observations of many experimenters, including E. Hubble.

2) Back in 1922-1924, A. A. Friedman solved the GRT equations for a non-stationary Universe that did not contain an "antigravity" term [8].

3) Any models of a non-stationary Universe based on the recognition of the universality of Hubble's law look doubtful.

4) The introduction of the anti-gravitational force into theoretical constructions contradicts the principle of universal simplicity of U. Occam, formulated in the XIV century: "entities should not be multiplied unnecessarily." Dark energy is certainly a redundant entity, since the laws of expanding Metagalaxy, as shown in this article, are simply explained within the framework of relativistic kinematics, in which there is no concept of dark energy.

5) If the acceleration of distant galactic star clusters cannot be neglected, then there is no need to talk about the influence of negative pressure on them, exceeding the gravitational attraction. "Galaxies don't scatter because some mysterious force pulls them apart. In the same way, a stone does not fly up because it is repelled by the Earth. Galaxies are moving away from each other because they were scattered by the Big Bang in the past."[8].

3. Conclusions.

The main results of the work done are as follows:

1) Mathematical expressions approximating the time dependence of the velocity of an object moving away from a stationary observer with constant acceleration and the equation of motion of this object are proposed. Thus, logically justified additions were made to the classical relativistic kinematics, which indicates that the stated purpose of the study has been achieved.

2) These additions are practically significant. They made it possible to prove the universality of the relativistic "twins paradox" and calculate the acceleration of the observed expansion of the Metagalaxy. It turned out that this acceleration is vanishingly small, so the hypothesis of the existence of dark energy cannot be considered convincing.

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DEVICE FOR CONVERTING AIRSPACE INTO ELECTRICAL ENERGY

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Abstract. *The article is devoted to devices for converting airspace into electrical energy and great enthusiasts of this idea, who are pursued by creative and purposeful people who want to improve the well-being of all mankind from the energy of our planet in the airspace. We know that we are surrounded by an ocean of energy surrounding our planet, but the problem is that it is very difficult to get it, since the potential of this energy, which is in large quantities, is highly dispersed in a vast space. However, if this task is now very difficult to solve due to big problems and high cost, then scientific discoveries and inventions in this area make an invaluable contribution to science, where new inventions based on these scientific discoveries can be used in other technical developments.*

Keywords: *airspace transformation device, environment, environment energy, Nikola Tesla, air environment energy.*

Since ancient times, humanity has received energy from the space of our planet, first in the form of burning wood, coal, oil. As progress increased and new inventions appeared, humanity began to receive energy from wind currents and water currents. Further, with increasing progress and the introduction of technology, energy began to be obtained from sunlight and nuclear reactions. This entire ocean of energy surrounding our planet can be used for the benefit of all mankind, but it must be treated with care.

Currently, a device for converting airspace into electrical energy is most often called a "fuelless generator", but there are no such generators in the world. In this case, the energy from the air flows of the environment from the airspace conversion device generates electrical energy and therefore the expression "fuelless generator" is not relevant in this case.

It must be remembered that many of the discoveries of great scientists happened suddenly, and their original idea was not given much attention. However, other inquisitive scientists continued research in these areas and found something new,

not related to this discovery of phenomena, which found their application in other areas of science and technology. For example, let's take the discovery of the Italian physicist, physiologist and inventor of the direct current source Alessandro Volta, who at the end of 1799 discovered that when two solid materials come into contact, a potential difference appears in the contact area, called the contact difference. However, at that time, this discovery did not find its application. After 22 years in 1821, based on the discovery of Alessandro Volta, the German physicist Thomas Johann Seebeck became the discoverer of another more significant scientific discovery based on the receipt of thermoelectric phenomena (in the copper-bismuth pair), built a thermocouple and used it to measure temperature, which are now widely used in instrumentation. This phenomenon of nature is based on the known laws of physics, which are time-tested and tested on our planet.

It should be emphasized that the thermoelectric current arises not only when dissimilar metals are joined, but also in a closed homogeneous conductor, if there is a temperature gradient, since a potential difference appears in each homogeneous conductor, the ends of which have different temperatures.

On the basis of these scientific discoveries, two hundred years later, a mechanism was discovered for the emergence of the Sun's magnetic field, a means of ensuring the rotation of the outer shell of the Sun's surface and creating around it the acceleration of the free fall of bodies in space. The means that ensures the rotation of the outer shell of the Sun's surface includes the interaction of prominences consisting of hot plasma interacting with the surface of the Sun and cosmic cold, which form strong thermoelectric currents, strong magnetic fields and create not only the mechanism of rotation of the outer shell of the Sun's surface, but also the acceleration of free fall bodies in space around our star. The magnetic field of the Sun, its rotation and the formation around it of the acceleration of free fall of bodies in space was popularly described in the journal "Actual Problems of Modern Science" No. 6 for 2022.

From this it must be concluded that any currently insignificant discovery that has not found its application at this time may be useful in the future for other more significant scientific discoveries and inventions of mankind.

It should be emphasized that before the invention of the device for converting air space into electrical energy by Nikola Tesla, at that time there were many new discoveries related to the transmission of energy over a distance in the form of electromagnetic waves, which are attributed to three different scientists. In Russia, it is believed that the Russian scientist and inventor Alexander Stepanovich Popov did this, in Europe the authorship is given to the Italian radio engineer Gugliermo Marconi, and in the USA they are sure that the Serbian scientist in the field of electrical engineering Nikola Tesla did this. However, there is an indisputable fact that, as a result, this invention and a description of a device that transmits

an electrical signal through airspace got on the pages of the Russian Physico-Chemical Society and was translated into all major European languages, where already in March 1896, this device managed to transmit a meaningful radio signal to a distance of 250 meters. A serious test of the technician A.S. Popov took place in 1899, when the battleship "General-Admiral Apraksin" pierced its side in the Gulf of Finland shortly before the invention of an apparatus for using radiant energy by Nikola Tesla.

However, let us return to the first invented apparatus, which received energy from the atmosphere of our planet. The official name of the patent under No. 685,957 issued on March 21, 1901 in the United States was "Apparatus for the use of radiant energy", where the famous Serbian scientist in the field of electrical engineering Nikola Tesla was its author.

Scheme of the apparatus for using radiant energy Nikola Tesla.

Figure 1 shows an apparatus for the use of radiant energy by Nikola Tesla, consisting of an energy space of air 1 interacting with a receiver 2 consisting of a conductive material that is electrically connected through a container 3 with the soil of our planet 4. The lower and upper base of the capacitor 3 through the conductor 5 and the conductor 6 having the contact terminals 7 is connected to the contact terminals 8 of the load source 9.

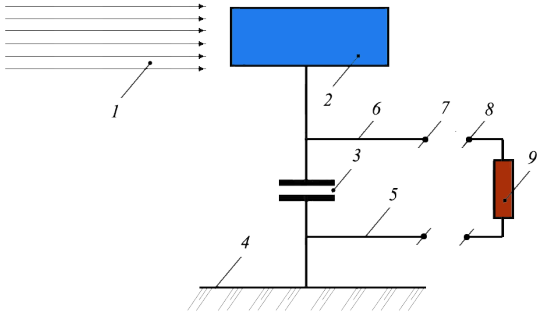

Figure 1

The principle of operation is to receive electrical energy by the receiver 2 from the energy space of the air 1. Next, the electrical signal enters the upper terminal of the storage capacitor 3, the outlet wire 6 and through terminal 7 interacts with terminal 8 of the load 9 and through conductor 5 enters the soil of our planet 4. Depending on the temperature differences between the air and the soil of our planet, thermoelectric currents can form in this generator, as mentioned earlier.

At present, after modern scientific discoveries, it is possible to explain the mechanism for the formation of mobile electrons from the air environment of

our planet, which is popularly described in the Scientific and Practical Journal "Higher School", No. 6 for 2021, page 39. Infiniti Publishing House, Ufa and the mechanism of education thermoelectric currents from the air environment of our planet, which was popularly presented in the information and analytical magazine "Actual Problems of Modern Science", No. 3 for 2021, page 66. Sputnik + Publishing House, Moscow.

One can fully agree with these statements and this invention, however, this invention does not allow obtaining significant power for use even in the household. To get more power from the device for converting airspace into electrical energy, it is necessary to use large areas of the receiver of electrical energy. After the invention of the device for the use of radiant energy by Nikola Tesla, there were many followers using more advanced materials and technologies, but the main problem was, is and remains creating a large area of the energy receiver from the air currents of our environment, without increasing its cost. However, this invention was not forgotten and many other scientific discoveries and technical developments came from it.

To these scientific discoveries, one can add mathematical evidence for the existence of cosmic ether or the substance of outer space, as presented in the information and analytical magazine "Actual Problems of Modern Science", No. 1 for 2021, page 33. Sputnik + Publishing House, Moscow. Registration certificate PI No. FS 77-39976 ISSN 1680-2721.

In conclusion, we can say that our material world is very diverse and all the processes performed in it from random circumstances that occur in time affect one another to a different extent, therefore a new theory of multifaceted dependence is put forward. In this world, everything is intertwined, and one natural phenomenon is dependent on another to a different extent. More active material bodies dominate less active material bodies, therefore there cannot be independent and constant constants, laws or physical quantities. For example, the new law of gravitational attraction and cosmic interaction between two material bodies located in the space of the Solar System or another system is closely related to the new law of gravitational attraction of one material body located in the space of the Solar System to the central star of the Sun. At the same time, the laws of gravitational attraction and cosmic interaction are in constant dependence on the new law of activity of a material body located in space and the new law of free fall acceleration of bodies in space. And the listed laws are closely connected with the new law of energy between two material bodies that are in the space of the solar system and the new law of energy of one material body located in the space of the solar system, to the central star the Sun and many others...

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SUSTAINABLE SOCIO-ECONOMIC DEVELOPMENT AT VARIOUS TERRITORIAL LEVELS

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Abstract. *The concept of sustainable development is considered for different spatial levels: regional and local. Sustainable socio-economic development is understood as the stable development of a certain spatial formation: a country, a region, a settlement, balanced in the economic, social and environmental spheres. At the local level, structurally the most complete, complex and integral formation is a separate settlement. Its sustainable development is characterized by a stable increase in the totality of economic, social and environmental indicators. At different spatial levels, sustainable socio-economic development is closely interconnected. Development impulses are transmitted from the local level to the regional ones through the links of spatial structures. At the same time, the interrelations and dependencies in the sustainable development of local and regional levels have not been studied fully and constructively.*

Introduction

The sustainable development strategies that have been developed recently are generally focused on different spatial levels, both local and regional. The main theoretical provisions for achieving sustainable development, first of all, were developed for the level of individual countries [1–5]. Separate developments are aimed at the problems and prospects for achieving sustainable development at the local and regional levels [6–13]. A number of works considered approaches to sustainable development in coastal regions [14, 15].

It should be noted that in general, sustainable development at different spatial

levels is interconnected. Development at local levels almost always depends on regional levels, and the development of a particular region includes developing local entities. However, the interrelations and dependencies in the sustainable development of local and regional levels have not been studied fully and constructively. These questions form the focus of this article.

Main part

Sustainable socio-economic development is understood as the stable development of a certain spatial formation: a country, a region, a settlement, balanced in the economic, social and environmental spheres. Structurally, the most complete, complex and integral formation at the local level is a separate settlement. The state of sustainable development of the settlement should be characterized by a stable increase in its economic, social and environmental indicators. At the same time, the settlement, as a rule, is not a closed system, it is connected both with the near territorial and water area - for coastal settlements - the environment for the use of natural resources, including land, water, forestry, and construction. It also houses recreation zones for the population, as well as zones for the spread of technogenic, anthropogenic impacts of the settlement on the environment. In addition, economic ties are often established between settlements by obtaining raw materials, semi-finished products and components for various activities, as well as by marketing their products and services. Thus, any settlement is always included in the system of regional markets for various resources and finished products. In addition, migration processes of population movement, as well as nature management relations, are realized near the settlement with the surrounding territory.

Therefore, if we identify and evaluate the main cycles of economic development - the chains of individual activities; social - human life cycles; environmental - the use of natural resources and the removal of man-made waste into the environment, it can be seen that all of them are more fully closed at the regional level. At the same time, the main impulses for sustainable development are laid down and implemented at local levels - in the structures of individual settlements. This is the formation of various parts of the industrial and social infrastructure that ensure the livelihoods of the population, types of economic activity that provide employment and living standards, as well as the whole range of relationships with the natural resource environment.

For the formation of a certain permanent population and all these structural elements of the settlement, as well as for their stable and balanced development, the settlement is included in the structures of regional development. Thus, the links and elements of local structures through spatial development are associated with regional development, moving to the regional level.

Interrelations of development at the local and regional levels are carried out through the following links of spatial structures:

1. Transport links - provide entrances to the settlement and exits from it;

2. Links of market structures - establish economic ties to obtain resources, materials, etc. to ensure the functioning of the infrastructure and various activities, for the sale of finished products and services;

3. Links of external structures of nature management - for the receipt and use of natural resources, as well as - the withdrawal of technogenic and anthropogenic waste into the environment;

4. Links of migration processes - from commuting labor migration to inter-district population movements. (fig. 1).

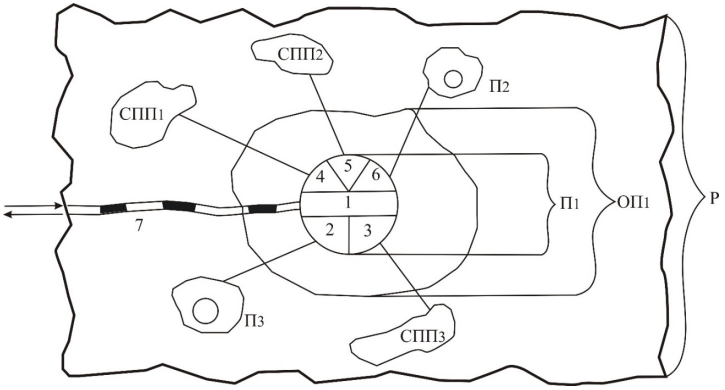

Figure 1. *Connections of local and regional levels in spatial development.*

Legend:

S_1 – central settlement, incl. 1 – population, 2 – production infrastructure, 3 – social infrastructure, 4, 5, 6 – enterprises of the main activities, 7 – external transport link.

TS_1 – territorial (aqua-territorial) environment of the settlement S_1; S_2 and S_3 – other settlements directly connected by transport links with S_1; SNM_1; SNM_2 ; SNM_3 – territorial nature management structures directly related to S_1; R - regional level.

Thus, sustainable development, as stable growth and qualitative increments of all structural elements of the S_1 settlement, depends on their interactions reaching the regional level. For a more rigorous assessment of the links and dependence of the sustainable development of the settlement - at the local level from the regional one, it is proposed to use the method of successive elimination of individual structural links connecting the local level with the regional one, including links with other settlements - S_2 and S_3, as well as - territorial links of nature management - SNM_1, SNM_2, SNM_3 and others.

On the basis of appropriate calculations, the ability of the settlement S_1 to function without these links is determined, including with the preservation or reduction of socio-economic and resource-environmental characteristics. On the basis of such calculations, certain limitations in sustainable development can also be established - as some limiting values in the use of natural resources or - in the removal of man-made waste into the environment, in which the socio-economic and environmental indicators of development deteriorate sharply. At the same time, more complete assessments of restrictions can be established at the regional level.

The sustainable development of territorial and sectoral structures of the economy as a whole - as combinations of homogeneous types of activities within a certain territory - should cover the entire spatial production system - from a separate economic point (settlement) to their regional combinations and the entire national economic complex of the country. Starting to manifest itself from the moment and levels of formation of individual settlements (towns and cities), territorial-branch structures move to regional levels (municipal formation; fractional economic region; meso-region: Oblast, Krai, republic; large mega-region; etc.). Separate links of the territorial and sectoral structures of mezarayons and mega-regions can enter the international regional markets for goods and services. At the same time, at any hierarchical level of changes, a stable combination of structural elements is preserved, consisting of functional blocks: specialization, production and population services. In the territorial aspect, sustainability is manifested in the ability of territorial-sectoral structures to form various linear-nodal combinations [16].

In the Far Eastern megaregion of Russia, regional and local territorial and sectoral structures are distinguished, consisting of manufacturing enterprises and organizations, the combinations of which form spatial systems of different ranks: regional (territorial and sectoral structures of the economic megadistrict - correspond to the federal district of the Russian Federation, meso-district - to the subject of the Russian Federation, micro-district - to the municipal district and their combinations) and local - territorial and sectoral structures of the economic node (urban municipal district), economic point (settlement).

As part of these spatial systems, the elements of the territorial and sectoral structure (enterprises and organizations of various industries and types of economic activity) perform various functions, depending on their role and place in the territorial division of labor (specialized, auxiliary, additional, servicing, etc.) [7, 16]. Combinations of homogeneous elements (industries, types of economic activity) form the sectoral structure of the region. Territorial and sectoral combinations of economic points, economic nodes in the composition of economic regions of different ranks form the territorial structure of the region - economic zones, belts, nodes, their groupings, etc.

The coastal areas are characterized by the development of maritime activities that focus on the natural resources of the ocean - biological, oil and gas resources of the shelf, recreational. The use of maritime transport provides a quick access to the world markets for goods and services [14, 15].

We have assessed the levels of socio-economic development of individual settlements and municipal districts.

The general goal of the development of any municipality is to increase the level and quality of life of the population living in it, on the basis of sustainable socio-economic development. To achieve this goal, it is necessary to solve a set of problems related to the rational use of existing economic and geographical factors (natural resource, demographic, social, economic, scientific and technical, environmental, spatial, etc.). The most important problem is to overcome differences in the levels of socio-economic development of individual municipalities, the presence of which negatively affects the quality of life of the population in less developed municipalities.

In the subjects of the south of the Far East, a set of municipalities has formed - districts and settlements, which differ significantly from each other in terms of the level of socio-economic development (population, production potential, industrial and agricultural output, etc.). Each municipality (urban district, municipal district and its settlements) develops on the basis of their combination of favorable and negative factors, which is reflected in the specific demographic structure and dynamics of the population and economy, nature management features, and in the territorial and sectoral structure of the economy.

Municipal districts differ significantly in terms of their territory and population, in large urban districts the main socio-economic potential of the region is concentrated. Rural municipal areas often have a low population density (compared to municipalities located in the European part of the country).

An important factor in the development of municipalities is the natural resource potential of the territory (availability of mineral resources, land resources, water resources, timber and bioresources of the forest and resources of coastal waters). The structure of the economy, the level of income of the population, as well as the prospects for their sustainable development largely depend on the territorial combinations of these resources available in municipalities.

To characterize the socio-economic situation of municipalities, we have chosen a set of the following available statistical indicators: 1) population dynamics; 2) wages and employment of the population; 3) characteristics of the budget (own revenues and their structure, share of social spending); 4) the volume of agricultural production; 5) investments; 6) volumes of housing construction; 7) the volume of shipped goods of own production (industry).

An analysis of the totality of indicators for urban districts made it possible to combine them according to the level of socio-economic development into the following groups.

1. Urban districts-leaders. These are the administrative centers of the subjects of the south of the Far East - Vladivostok, Khabarovsk, Blagoveshchensk. They concentrate the main socio-economic potential of the subjects and have high development rates.

2. Urban districts with a high level of development compared to most urban districts of the subjects of the south of the Far East. As a rule, these are urban districts with a large population and a favorable socio-economic situation: Birobidzhan, in the Khabarovsk Krai - Komsomolsk-on-Amur; in Primorsky Krai - Artem, Nakhodka, Ussuriysk; in the Amur Oblast - Belogorsk, Svobodny, Zeya.

3. Urban districts with little socio-economic potential. These are small urban districts (in terms of population), in a significant part of which there is a depressive nature of the socio-economic sphere.

Our assessment of municipalities in terms of their level of socio-economic development, in general, allows us to note that the levels of development of settlements basically correspond to the level of development of municipalities - urban districts and municipal districts - in the regions of the south of the Far East they are distinguished by a wide variety of indicators of the standard of living of the population, social sphere and economy than in the northern regions.

Conclusion

Achieving sustainable development at the local level - the level of individual settlements - is possible only if there are relationships with the regional level, including in the economic, social, resource and environmental spheres. Such relationships are established in the process of spatial development, through the formation of structural links that connect this settlement with other settlements and nature management structures within significant territories and water areas of the districts.

To assess the links and dependence of sustainable development at the local level with the regional, it is necessary to calculate options for the possible exclusion of individual links between local and regional structural links. At the same time, limitations in sustainable development are also determined. In a more complete form, sustainable development is possible only at the regional level.

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MANAGEMENT OF THE ECOLOGICAL STATE OF THE TERRITORY USING THE INTEGRAL INDEX OF ECOLOGICAL WELL-BEING OF THE TERRITORY (ON THE EXAMPLE OF THE PERM KRAI)

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Abstract. *The deterioration of the ecological state on the territory of the Perm Krai is associated with an intense technogenic impact on the environment. Currently, in the practice of nature management there is no single, generally accepted method for the integral assessment of these impacts, and therefore the managerial decisions made are usually aimed at solving particular environmental problems (for example, the "Clean Water" program). The article proposes a method for calculating the integral index of environmental well-being (IES). It is based on technogenic impacts on all components of the natural environment with the obligatory consideration of the consequences of this impact on public health. The main results of using the methodology are given on the example of administrative-territorial units (ATU) of the Perm Krai: problem areas are identified for socially significant and priority environmental problems. The identified problems and established relationships between them and morbidity rates will make it possible to objectively outline environmental and socially significant measures aimed at improving the health of the population in the context of ATU and can be used in the development of environmental policy, and, consequently, in making management decisions.*

Keywords: *ecological state, Perm Krai, index of ecological well-being, social conditions, morbidity of the population, assessment of the state of the territory, management.*

Relevance. In 1972, the international public organization "Club of Rome" released the first report - the famous "The Limitsto Growth" - the results of mathematical modeling of the depletion of natural resources due to population growth [1]. The model contained 12 scenarios, five of which described a catastrophic decline in the population to 1-3 billion people due to excessive consumption growth, and seven scenarios were more favorable and relied on increasing environmental, demographic and social awareness of mankind. In the same 1972, the United Nations (UN) Environment Program was created, which initiated the discussion of environmental problems at the global level. The result is the global project "Sustainable Development" - a set of measures aimed at meeting current human needs while preserving the environment and resources, that is, without compromising the ability of future generations to meet their own needs. Sustainable development is possible with a balance of three main components: economic growth, social responsibility and environmental balance. The proposed methodology for the integral assessment of environmental well-being is aimed at maintaining the ecological balance.

Rationale for research. An integral part of the ecological balance is the rational use of natural resources. It involves such use of natural resources, in which the negative consequences of anthropogenic influence do not take place. In this regard, management issues related to the regulation of the interaction between the object (nature) and the subject (human) and the resulting subject-object relations are of particular importance [2]. In figure 1, they are presented in the form of blocks. The first includes objects that are the main subordinate components of nature: leading (geological structure and relief; climate, surface and groundwater) and driven (soils, vegetation and wildlife). The second block includes the subjects and their possible actions on the objects included in the first block. It can be represented by private blocks, including natural and technogenic components, which affect the object in two ways: directly and indirectly (for example, the surface runoff of suspended solids may increase due to plowing of the territory). The third block includes a system that has changed as a result of its functioning, the implementation of object-subject relationships in rocks, exogenous processes, changes in the main meteorological characteristics, indicators of hydrodynamic regimes, etc. This block, being the result of object-subject relations, does not remain passive: its components, in turn, affect the object (feedback), forcing the latter to function under changed conditions (fig. 1).

These blocks can be considered as a combination of the basis (I block-object) and factors (II and III blocks - the subject and subordinate components, interconnected by relationship, interaction and regulation). The role of the second and third blocks will depend on the nature of the impact on the object. If the subject includes not only a natural, but also an anthropogenic component, which exceeds

the natural one in terms of influence and leads to environmental disturbances, then the system practically becomes open, i.e.

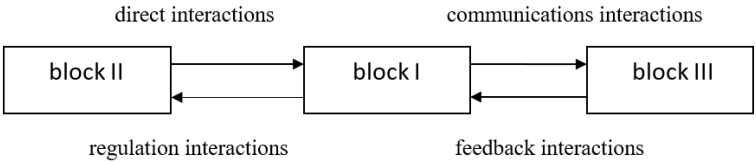

Figure 1. *Scheme of functioning of the natural system*

subject-object connections are weakened (fig. 1). The transformation of an object occurs mainly due to the transition of quantitative changes into qualitative ones.

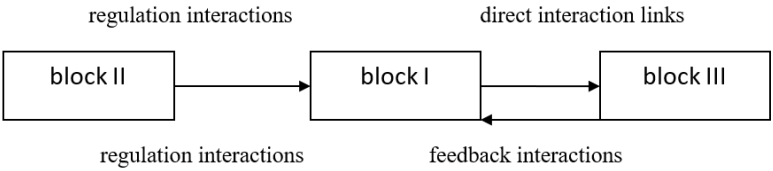

Figure 2. *Scheme of functioning of the geosystem under strong anthropogenic impact*

As a result of these changes, the system changes the initial direction of its development and loses its ecological balance. The more the object changes, the closer the system approaches the ecological crisis (problems of the Aral, Sevan, Baikal, etc.). To eliminate crisis situations, a person is forced to create another type of connection - between blocks I and III - adaptation connections (pig. 3).

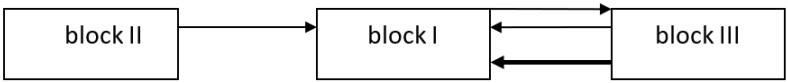

Figure 3. *Scheme of the functioning of the system in the presence of connections of the device*

Most of the measures currently being developed (flow diversion, construction of treatment facilities, dams in the Caspian Sea, etc.) only make it possible to adapt the changed conditions (block III) to the natural environment (block I). However, as practice shows, adaptation ties do not always guarantee the elimination of

environmental crises. Therefore, it is necessary to create control links that close the system. They should be formed simultaneously with the emergence of the natural-economic system and regulate the relationship between man (block II) and nature (block I) in such a way that the functioning of the system being created does not lead to a violation of the ecological balance (fig. 4).

Figure 4. *Scheme of functioning of a closed natural-economic system in the presence of control links (⟵)*

Consequently, systems can be protected from crisis ecological situations only by the connections of management, although at present, connections of adaptation predominate in the already established natural and economic systems. The study of the management process in terms of its functions allows you to set the scope of work for each of the functions, form the structure and organization of the management system. Each management function has its own structure, determines the content of the work, which is subject to a clear sequence of actions regulated by legislative acts. Management functions are very diverse. For example, the main ones for water management are: organization of water use and water consumption, planning of acceptable use of water (its quantity and quality), (forecasting, modeling, programming), administrative activities (administration), including the coordination of all water users and water consumers, motivation, coordination (coordination) and control over the fulfillment of tasks and monitoring the state of water resources.

Thus, management functions define activities aimed at organizing the implementation of measures to manage an object (for example, a river basin) or territory (for example, a city), and the logical sequence of work is the essence of management technology. The main purpose of the managerial function has two components: 1) analysis of the state of the system (for example, a river basin), control of its main parameters (flow rate, concentration of elements of chemical composition, etc.), quantitative determination of those factors that bring the system out of equilibrium (technogenic loads); 2) determining the scope of measures aimed at optimizing the management process (preserving the quantity and quality of water).

The described scheme for the formation of a managerial function is applicable to any components of the natural environment and territories, but its structure will differ depending on the structure of the administrative management of the study area (ATU). We propose to make management decisions at the level of large

territories (for example, Perm Krai), based, firstly, on the EWBI (environmental well-being index), and secondly, taking into account the social conditions of life of the population and its health.

By EWBI, we mean such a state of the territory in which the physiological, economic and medical and social needs of the population are satisfied, ensuring the health of the population, and at the same time there is no or minimized negative impact on the natural environment. The index of ecological well-being is a complex indicator. It consists of partial indices (PI) that characterize the intensity of impacts on individual natural components, which, in turn, are determined through relative coefficients - K, showing the impact of any factor on one component of the natural environment.

The calculation of EWBI includes several stages and is detailed in [10]:

1) ***Choice of calculated indicators:*** flow rate and volumes of wastewater discharges; volumes of emissions of pollutants into the atmosphere from stationary and mobile sources; volumes of waste generation, humus content in soils, proportion of acidic soils, areas of water and wind erosion and density of ravines, forest cover of the territory.

2) ***Determination of the conditional norm of exposure.*** As such a criterion, we propose to use the "conditional norm", corresponding to 50% of the provision of the indicator of technogenic impact according to Krai [13].

3) ***Calculation of relative coefficients*** for the selected calculated indicators. The relative coefficient is determined by formula (1), if with its increase the positive role in the formation of the natural component grows (for example, water supply), otherwise (for example, emissions into the atmosphere) - according to formula (2).

$$C_i = \frac{C_n}{C_f} \quad (1), \qquad C_i = \frac{C_f}{C_n} \quad (2)$$

where (C_i) – relative coefficient in i-th ATU; Cf- the actual value of the analyzed indicator in the i-th ATU; Cn – its conditional norm (criterion) corresponding to its 50% provision on Krai.

4) ***Calculation of partial indices of natural*** environments is carried out according to the formula (3):

$$I_{zi} = (C_1 + C_2 + \cdots C_n)/n \quad (3)$$

where I_{zi} - private index of the natural environment; *z*–natural component; *i* – ATU; C_1, C_2, C_n –relative coefficients, *n* - the number of terms.

5) ***Integral EWBI calculation***. The index of ecological well-being was defined as the geometric mean between the partial indices of natural components:

$$I_i = \sqrt[4]{I_{wat} \times I_{air} \times I_{soil} \times I_{for}} \quad (4)$$

where I – EWBI in i-volume ATU; I_{wat}, I_{air}, I_{soil}, I_{for} – private indices of natural components.

6) ***The assessment of the ecological state of ATU according to EWBI*** is carried out on a five-point scale: favorable (1.0–1.5 points), acceptable (1.51–2.0 points), satisfactory (conditional norm) (2.01–2.5 points), tense (2.51–4.0 points), crisis (more than 4.01 points) [10].

The developed criteria were used as the basis for the construction of the map "Assessment of the ecological state of the Perm Krai" (fig. 5).

The assessment of social conditions and morbidity of the population was carried out according to private indices (PI_{soc} and PI_{acc}). When studying social conditions, the following indicators were used: provision of the housing stock and the average level of wages; availability of doctors and nurses, population density. The health of the population was assessed in terms of general morbidity and environmentally significant morbidity for various nosological forms. The results of the calculations are reflected on the maps: "The state of the social conditions of life of the population" and "Distribution of the general morbidity of the population" (fig. 6, 7).

Correlation analysis showed that there is a high relationship between EWBI and general morbidity rates in adults and children aged 0 to 14 years (r_s = 0.72–0.79, p = 0.95) and noticeable (r_s = 0.63–0.67, p=0.95) – in children of the first year of life, including incidence rates of such environmentally significant diseases as diseases of the blood and blood-forming organs, including anemia, respiratory diseases and congenital anomalies. The role of social conditions in the formation of general morbidity is high both in the adult population and in children (r_s = 0.88-0.89, p = 0.95).

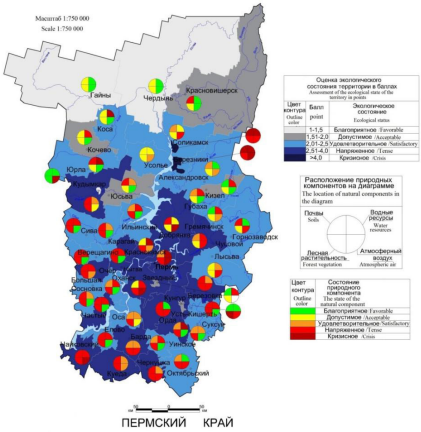

Figure 5. *Assessment of the ecological state of the Perm Krai [10]*

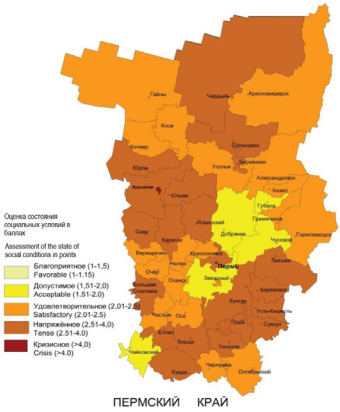

Figure 6. *The state of social living conditions of the population [10]*

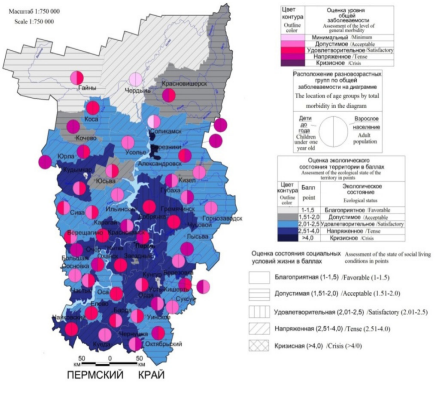

Figure 7. *Distribution of the level of general morbidity [10]*

Table

Spearman rank correlation coefficients (r_s) between social conditions, EWBI and population incidence rates

General morbidity rates	Spearman's rank correlation coefficients (r_s)	
	EWBI	Social conditions
General morbidity of the adult population	0.76±0.10	0.88±0.07
General morbidity in children (0–14 years)	0.72±0.10	0.80±0.07
General morbidity of adolescents	0.79±0.09	0.89±0.07
The general incidence of children under one year of age for some nosological forms of diseases:	0.64±0.11	0.89±0.07
- diseases of the blood and blood-forming organs	0.66±0.11	0.89±0.07
- anemia	0.66±0.11	0.80±0.08
- respiratory diseases	0.67±0.11	0.89±0.07
- congenital anomalies	0.63±0.11	0.86±0.08

Thus, the incidence of different groups of the population (except children of the first year of life) is equally affected by environmental and social conditions, and in children of the first year of life, social conditions play an important role (r_s = 0.86–0.89, p = 0.95) (tab.).

Conclusions

1. When managing the ecological state of the territory, EWBI can be used as the main indicator. The method of its calculation, based on the chain: "relative coefficient (the impact of one factor on one component of the natural environment) - partial index (intensity of all impacts on a particular natural component) - EWBI of the territory (geometric mean value of partial indices within the study area"), allows give a quantitative and qualitative assessment of the ES of the Krai territory, highlighting the main environmental problems; and private indices, in addition, - an assessment of the territories according to the state of social conditions and the health of the population.

2. On the basis of calculations and zoning, problem areas are identified for socially significant and priority environmental problems. It has been established that a tense and crisis ES has developed in 31 and 6% of the administrative territories of the Perm Krai, respectively, and in terms of social conditions - by 47 and 2%, respectively.

3. In the formation of the health of the population, both social conditions and the ES of the territory of residence are almost equally involved. The identified problems and established relationships between them and morbidity rates will make it possible to objectively outline environmental and socially significant measures aimed at improving the health of the population in the context of administrative-territorial units and can be used in the development of the environmental policy of the Perm Krai.

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SHORT PEPTIDES AS REGULATORS OF ROOT DEVELOPMENT IN SOME SPECIES OF THE *SOLANASEAE* FAMILY

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Annotation. *At present, much attention in agrobiotechnology and agriculture in general is the search for new, effective growth regulators that can provide consistently sustainable yields, including under abiotic stress. It is shown that short peptides have a stimulating effect on the root system of Nicotiana tabacum and Solanum lycopersicum. Depending on the structure of the peptide, an elongation of the main root or an increase in the length of the root hairs was observed. Such a tissue-specific action of short peptides will allow targeted regulation of plant growth and development, which is relevant for agrobiotechnology. Salt stress is one of the most common stresses in plants, which causes great damage to agriculture. Short peptides have been shown to be able to protect the plant from the toxic effects of sodium chloride. The protective properties of short peptides can help increase crop yields.*

Keywords: *short peptides, roots, root hairs, salt stress, Solanaseae family.*

Introduction

Peptides are involved in extensive and diverse regulatory network that controls the growth and development of plants and animals. Secreted peptides (containing from 2 to 100 amino acid residues) play an important role as regulators of intercellular interactions, physiological activity, and responses to various

environmental influences and signals. They can trigger or inhibit a variety of genetic processes and biochemical reactions in the cell. Roots are critical to plant development as they link the underground and above ground systems and extract water and nutrients from the soil. The ability of roots to absorb minerals and water from the soil and respond to environmental changes depends on the architecture and size of the root system.

Results and discussion

Based on the obtained results, we see that the length of the root of tobacco seedlings grown on the medium with the AEDL peptide is 2 times higher than the root length of the control seedlings, and the height of the shoots of the experimental plants is 20% higher than the control ones (Figure 1). Under salinity, these differences persist. The concentration of sodium chloride 150 mm leads to a significant inhibition of the development of the root system in tobacco seedlings. With the combined presence of the peptide and sodium chloride in the nutrient medium, the normal development of the root system is observed. Biometric data indicate an elongating effect of the peptide AEDL on both root length and seedling height. It can be assumed that short peptides are able to neutralize the toxic effect of sodium chloride. The concentration of the peptide AEDL in the medium used in the experiments is very low (10^{-7} M), from which it can be concluded that its action is similar to that of phytohormones.

Figure 1. *28-days tobacco seedling growth without and with additives*

Using the method of fluorescent microscopy, the localization of FITC - AEDL was determined in the region of the zones of stretching and differentiation. In the meristem zone, the glow was insignificant. In some cells of the tobacco root, a particularly intense fluorescence is observed in the nucleus (Figure 2).

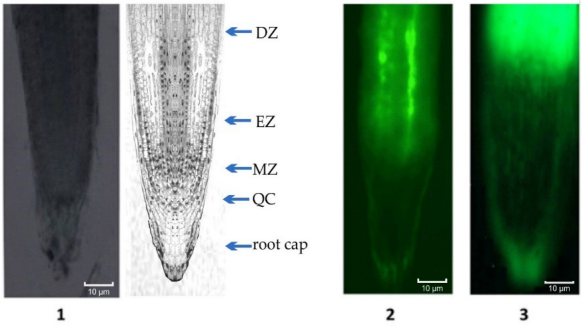

Figure 2. *Visualization of FITC-labeled AEDL in tobacco roots. 1 - root incubated with FITC; 2- root incubated with FITC-AEDL; 3 - root incubated with FITC-AEDL with 3 x magnification of MZ. DZ- zone of differentiation, EZ- zone of elongation, MZ – zone of meristem, QC - quiescent center.*

Therefore, the studied peptide is able not only to penetrate into the nuclei, but also, apparently, to accumulate in them to a significant extent compared to the cytoplasm. Electron micrographs show changes in plant nucleus density when grown with AEDL and exposed to salinity. Thus, the peptide AEDL is likely to be able to influence the structural organization of nuclei and chromatin morphology and cause changes in the expression of a number of genes associated with development and differentiation.

Root elongation in plants can occur either by increasing the process of stem cell differentiation in the meristem, or by weakening the cell wall in the zone of root elongation. The continuous growth and development of plants is controlled by meristem, which contain pools of stem cells [1]. The size of the meristem is directly related to the rate of root growth. The division of stem cells and their differentiation are coordinated by intercellular signaling. Balancing the rate of proliferation and differentiation of stem cells is a key factor in determining root growth, since root elongation is largely determined by the number of cell divisions and their subsequent cell elongation.

Stem cell identity is determined by signaling from a group of cells that organize a calm center (QC) in which the WUS homeodomain functions [2]. Loss of WUS function leads to stem cell differentiation [3]. Conversely, *WUS* expression in primordial vegetative organs induces ectopic stem cell identity [4], indicating that *WUS* expression must be tightly controlled to maintain the required number of stem cells. Thus, stem cell homeostasis requires a dynamic feedback loop. It is known that a small secreted CLV3 polypeptide acts in the extracellular space as a negative regulator of *WUS* expression [5].

According to fluorescence microscopy data, the FITC-labeled peptide AEDL penetrates into the tobacco root and is localized mainly in the elongation zone and slightly in the meristem zone. However, it does not penetrate into the QC zone and the stem cell niche. It can be assumed that the peptide AEDL containing a hydrophobic leucine residue can bind to a hydrophobic leucine motif on the CLV1 receptor, which prevents the peptide from entering the stem cell niche. Binding of the peptide AEDL to the CLV1 receptor leads to the activation of the receptor complex, thereby limiting the stem cell population and activating their differentiation. At the same time, the formation of the peptide AEDL–CLV1 receptor complex does not allow the peptide CLV3 to penetrate into the meristem from the QC zone.

The expression of *WOX* genes in tobacco grown in the presence of the peptide AEDL, compared with the control variant, drops down to zero. This fact, according to the literature, indicates a decline in the population of stem cells and an increase in their differentiation. An increase in stem cell differentiation results in an elongation of the main root in *Nicotiana tabacum* grown in the presence of the AEDL compared to the control.

Plant cell walls expand or relax as a result of the process of molecular "creep", in which cellulose microfibrils and their associated matrix polysaccharides separate from each other [6]. Such molecular creep occurs only when the cell wall is loosened by expansins or other factors [7].

In *Nicotiana tabacum* the expression of the *EXPA3* and *EXPA5* are similar, in the control plants and in those exposed to the peptide AEDL. Thus, this suggests that the lengthening of the roots in the presence of the peptide does not occur due to the weakening of the cell wall in the elongation zone. A 50% decrease in *EXPA5* expression in the presence of a high concentration of sodium chloride is accompanied by a decrease in the length of the roots and their bending. However, in tobacco grown with the combined presence of NaCl and AEDL, there is a significant increase in the expression of both *EXPA3* and *EXPA5* (more than three times). Such an increase in the expression of expansin genes is probably due to the fact that the presence of NaCl led to a change in the structure of chromatin, it became more decondensed and accessible for the penetration of the peptide AEDL into chromatin and for the regulation of expansin expression. An increase in the activity of expansin genes contributes to the weakening of the cell wall, especially in the elongation zone, and thus to the elongation of the roots. Thus, the elongating effect on the roots of tobacco seedlings in the presence of the peptide AEDL and in the combined presence of the peptide AEDL and 150 mM NaCl occurs through different mechanisms.

Root hairs are of particular importance for plant growth and development, they are able to absorb sufficient amounts of water and nutrients from the rhizosphere

during drought and/or nutrient deficiency, interact with soil microfauna, and fix the root in the soil. Increasing the number of root hairs and their length may be one of the potential approaches to increase the productivity of crops under stress and their tolerance to depleted soils.

Short peptides GlyGly and GlyAsp and Gly penetrate the roots and their accumulation is tissue-specific with predominant localization in the root cap, meristem, extension and absorption zones. Peptides penetrate into the cells of the epidermis and cortex and show preferential localization in the nucleus than in the cytoplasm.

The mechanism of action of dipeptides and Gly differed depending on their structure and charge. Root hairs located in the root suction zone create a large surface area for the absorption of water and nutrients. Dipeptides and Gly have a marked effect on the development and elongation of tobacco root hairs. In the presence of peptides, the root hairs were longer, denser, and differed in the nature of pubescence compared to the control. In the presence of Gly, GlyGly, and GlyAsp peptides, root hairs differed in length, density, and pubescence pattern (Figure 3). Compared to the control, root hairs were 2, 4, and 6 times longer in the presence of Gly, GlyGly, and GlyAsp, respectively. In addition, root hairs treated with GlyAsp were more branched than those treated with other peptides.

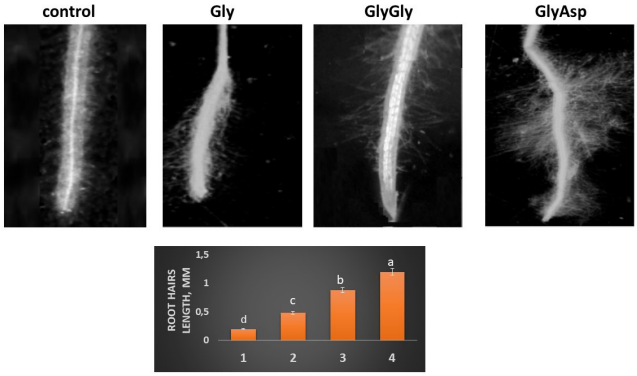

Figure 3. *Effect of peptides on the length, density and pubescence of root hairs of tobacco seedlings. 1- control; 2 - Gly; 3 - GlyGly; 4 - GlyAsp. The mean values (n=20) and their standard deviations are shown according to significant value, p<0.05. Different letters above the bars indicate significantly different values.*

Plants have systems for regulating the length of root hairs. The same cells contain genes that activate hair growth and genes that inhibit hair growth. These

genes are expressed simultaneously in the cell; however, activation of some genes and inhibition of others is observed at different stages of development of root hairs and under the influence of various factors.

In this study, two active complexes were considered. One of these complexes includes six genes (*CPC, ETC, GL2, GL3/EGL3, TTG*, and *WER*), three of which (*CPC, WER*, and *GL2*) are expressed in H cells along with *bHLH*, which acts as a linker. The *WER* gene suppresses the expression of the *CPC* and *GL2* genes in H cells, thereby initiating the formation and growth of root hairs. Another complex includes the *WER, CPC*, and *GTL1* genes, the latter inhibiting root hair growth (Figure 4). Activation of the *WER, CPC, bHLH54*, and *bHLH66* genes and inhibition of the *GTL1* and *GL2* genes could probably explain the elongation of root hairs in tobacco seedlings grown in the presence of Gly, GlyGly, and GlyAsp compared to controls.

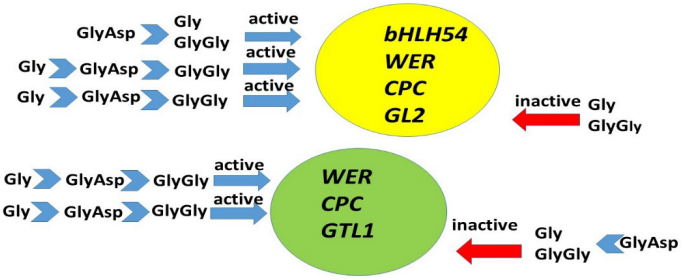

Figure 4. *Scheme of activation and inactivation of root genes*

Thus, despite the similar structure of the peptides, their effect on the growth of root hairs differed, most likely due to the fact that the neutral amino acid Gly and the dipeptide GlyGly, as well as the negatively charged dipeptide GlyAsp, bind to different motifs in functionally important proteins. Gene expression levels differed slightly between tobacco plants grown in the presence of GlyGly and Gly, most likely due to differences in binding constants between them and protein motifs. On the whole, the GlyGly and GlyAsp dipeptides, as well as the Gly amino acid, showed pronounced physiological activity and can be considered as positive regulators of root hair formation.

The effect of the peptides on the tomato *Solanum lycopersicum* was similar to their effect on the tobacco *Nicotiana tabacum* (Figure 5).

Figure 5. *20-days tomato seedling growth without and with peptides*

Our results on the use of exogenous peptides allow us to propose their use in agriculture as new promising environmentally friendly plant growth regulators. It has been found that structurally diverse peptides act differently on different organs of the same plant species, and moreover, the same peptides act differently on different plant species. Such a tissue-specific action of short peptides will allow targeted regulation of plant growth and development, which is relevant for agrobiotechnology. The tissue-specific action of short peptides makes it possible to control the growth of both the main plant root and its root hairs.

Materials and Methods

Seeds of tobacco *Nicotiana tabacum* L.or tomato *Solanum lycopersicum* were placed in flasks (150 mL) containing hormone-free Murashige–Skoog (MS) medium supplemented with or without peptides 10^{-7} M. Glass flasks were placed in a climatic chamber. Cultivation was carried out at 24 °C.

To determine the localization of peptides in root cells, the FITC-labeled peptides were used. Root tips (4–5 mm) were excised from tobacco seedling roots, and fixed in 4% paraformaldehyde for 1.5 h at room temperature. After three washes with phosphate-buffered saline, the root tips were mounted on glass slides and embedded in Moviol. Fluorescence was analyzed at a wavelength of 490 nm using Olympus BX51 microscope.

Information on the primary structure of *Nicotiana tabacum* genes was obtained from the National Center for Biotechnology Information (NCBI). Primers for these genes were designed using the NCBI Primer-BLAST web tool, and synthesized at Syntol. Real-time PCR was performed on CFX96 Touch Real-Time PCR Detection System (Bio-Rad) using a set of RT-PCR reagents and SYBR Green (Syntol). The calculation of the main statistical parameters was carried out according to STATAN program on a significance value $p < 0.05$.

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