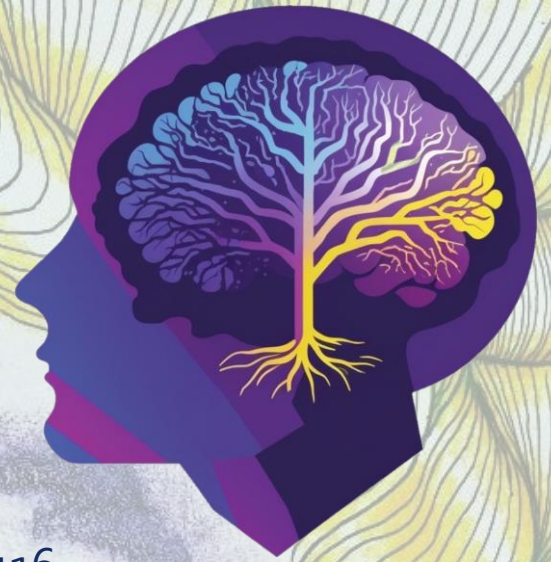


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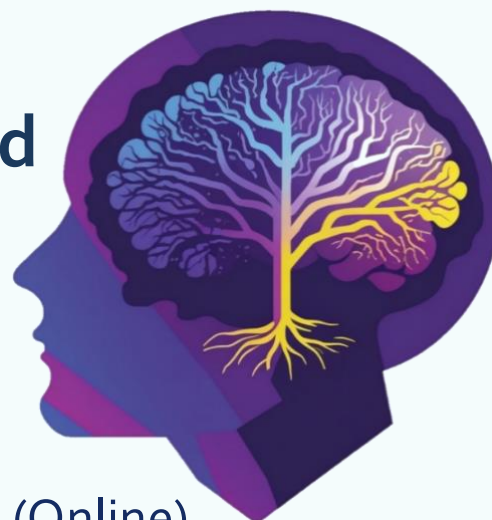
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Relationship of Some Psychophysiological Indicators With Individual and Typological Features of Young Men

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The success of studying at a university is largely determined by the compensatory-adaptive capabilities of the body to new social environmental factors. A change by a person of himself, his own attitudes and habitual behavioral stereotypes occurs. Changing the environment to meet a wide range of own needs is happening [1]. At the same time, the effectiveness of students' adaptation to the conditions of study at a university largely depends on their personal qualities. Extra- and introverted personalities react differently to problems. This has various consequences of the adaptation of the individual to society [2].

The aim of the study was to evaluate some psychophysiological indicators of young men depending on their individual typological characteristics.

The survey involved 60 second-year students of the Tver State Medical University. All students gave voluntary written consent to the upcoming examination.

The level of extraversion (introversion and neuroticism) was assessed using the Eysenck questionnaire; situational and personal anxiety (SA, PA) was assessed using the Spielberger-Khanin questionnaire; self-assessment of the current mental state was assessed by the method of well-being - activity - mood (WAM). The computer complex for psychophysiological testing «NS-psycho-test» was used («Neurosoft») [3].

Psychophysiological examination of simple and complex visual-motor reactions (SVMR, CVMR) was performed using a portable device PTD-1/30 – «Psychophysilogist» («Medicom MTD»). Nonparametric methods were used for statistical analysis in the Statistica 6.1 program. The critical level of significance is $p \leq 0.05$ in paired comparisons, it is $p \leq 0.017$, taking into account the effect of multiple comparisons.

According to the results of the study on the Eysenck personality questionnaire, the respondents were sincere in their answers to the questions. The number of points on the lie scale did not exceed five [4].

Extra-, intro- and ambiverts were identified as a result of the analysis of the features of individual psychological characteristics (32, 30, 38%).

In our study, the average level of neuroticism without significant differences in the examined groups was found among young men. The average degree of emotional stability of a person is characterized by calmness, poise, confidence, determination in the usual conditions, but a reduced level of resistance to the effects of pronounced adverse factors [5]. The influence of the severity of neuroticism on the functionality of the cardiovascular system was noted in the work of V.D. Perkhurova et al. [6].

Factors such as intro- and extraversion, neuroticism not only characterize the personality in the system of relations with the outside world and evaluate the individual in the context of his own



response to the environment, but also make it possible to indirectly judge the adaptive capabilities of a person [7,8].

According to the test results, the average level of PA and SA prevails in young men in groups of different personality types. In general, anxiety can be beneficial for a person and have a productive character. She is able to motivate people in a positive way. Its average level is optimal for the implementation of activities and contributes to the mobilization of efforts, adaptation to new conditions [9]. In our study, the PA value significantly correlated with the level of neuroticism ($r = 0.67, p = 0.0001$).

In general, the differences among individuals in the examined groups in terms of the level of PA are significant ($p = 0.03$). At the same time, the level of PA in introverts (Me = 42.40 (Q1 = 38.00; Q3 = 52.00)) is significantly higher than in extroverts (Me = 34.00 (Q1 = 28.50; Q3 = 40.50)) ($p = 0.01$). Similar data were obtained for SA (introverts: Me = 43.00 (Q1 = 33.00; Q3 = 50.00); extraverts: Me = 33.00 (Q1 = 26.50; Q3 = 39.00)) ($p = 0.01$). No significant differences were found with the ambivert group.

Features of personal characteristics, in particular extraversion-introversion, are one of the psychological sources of anxiety. The severity of the properties of introversion is accompanied by a higher level of PA and SA and vice versa [10]. In our study, a significant average negative relationship between these indicators was found among respondents ($r = -0.36, p = 0.009$; $r = -0.30, p = 0.033$).

The level of well-being, activity and mood among extra-, ambi- and introverts did not differ significantly and was in the range of medium and high values. This indicates a moderate and favorable state that has a positive effect on the psychological process of personality development, and, accordingly, on adequate behavior in society [11].

Evaluation of the functional state is possible not only by the values of individual indicators of WAN, but their ratios are important [3]. In our study, signs of fatigue using this method were found only in ambiverts. A decrease in activity and well-being in comparison with mood indicates this ($p = 0.016$; $p = 0.027$).

There is a relationship between individual typological features and behavior depending on the functional state of the central nervous system [12]. The parameters of visual-motor reactions are integral indicators of the properties of the nervous system.

In our study, there were no significant differences between the indicators of visual-motor reactions in the groups of subjects [13]. In general, the results of SVMR reflect the average level of activation of the central nervous system, the average speed and stability of reactions, and the stable state of regulatory mechanisms. The values of the mean reaction time were in the range of 212–257 ms, the standard deviation was 45–90 ms.

The mean reaction time of CVMR less than 405 ms and the total number of errors (ER = 1) indicate a higher average quality of test execution at a high reaction rate, an optimal combination of speed and error-free actions. A high level of operator performance was found in all subjects.

In our study, the levels of PA and SA were significantly higher in introverts. This is due to their personal characteristics. Significant differences of other psychophysiological parameters studied using methods such as WAM, visual-motor reactions were not found between the groups. All



subjects have a favorable current state, the same speed of reaction and the level of their operator performance. This allows students to work productively.

Keywords.Extroversion, introversion, ambiversion, anxiety, well-being, activity, mood, visual-motor reactions

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Using of the "Endoactivator" Device to Activate an Irrigation Solution in Endodontic Treatment: a Case Series

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Introduction: devices for activating of irrigation solution improve the cleansing of the root canal, as well as reduce postoperative sensitivity (Anand Susila and Joseph Minu, 2019). One of these devices is the EndoActivator, which creates wave vibrations in the root canal to improve the mixing of debris and irrigation solution and subsequent removal during rinsing (Margy Parih et al., 2019)

The purpose of the study: to evaluate the advantages of working with the EndoActivator device on the example of a series of clinical cases.

Materials and methods: five patients underwent endodontic treatment of chronic apical periodontitis. The treatment was carried out according to a standard protocol, instrumentation of root canals was carried out in CrownDown technique using rotating nickel-titanium instruments, irrigation was done with sodium hypochlorite, which was activated using an EndoActivator device, then calcium hydroxide was placed in the root canals for 14 days, after which the filling was carried out by the method of lateral condensation with gutta-percha pins and an epoxy-based sealer. After each visit, which included endodontic treatment, patients were asked to inform the doctor via messengers about the intensity of postoperative sensitivity (absent, low, medium, high). Restoration of the crown part was carried out using direct and indirect restorations, depending on the degree of destruction.

Results: None patient noted high postoperative sensitivity, two patients reported about low level, one patient noted sensitivity of medium intensity, other patients had no any postoperative sensitivity. In all clinical cases gradual healing of periapical lesion was observed at different follow-ups.

Conclusions: The following advantages of the device were revealed: convenient manipulation characteristics, effective evacuation of debris from the root canal, faster removing of dressing materials, which allows to shorten this stage. There were no cases of high postoperative sensitivity after treatment with this device in the presented case series.

Keywords: EndoActivator device, irrigation solution activation

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Puva Therapy and Darsonval Impulse Current in Psoriatic Onychodystrophy

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Target. With psoriasis, 50-70% of cases have onychodystrophy. This disease is difficult to treat and causes discomfort, anxiety, social maladjustment /1, 4/. These patients with nail lesions are shown to be treated with various drugs: local, systemic, intra-focal and radiation therapy /2/. This treatment is not always effective. Toxic, and in kidney disease, heart disease and other diseases, they are contraindicated /3/. Therefore, it is necessary to look for more gentle and effective methods of treatment.

In connection with the above, the purpose of our study was to increase the effectiveness of the treatment of psoriatic onychodystrophy with the use of a combination of PUVA therapy and the use of a pulsed sinusoidal current of supratoral frequency (D'Arsonval)

Material and methods. The study included 75 patients with psoriatic onychodystrophy, which were divided into 3 groups: the first group (25 people) received drug treatment in accordance with clinical guidelines for this pathology; the second group (25 people) received PUVA therapy (systemic); the third group (25 people) received combined physiotherapy, including sequential exposure to D'arsonval pulsed current in the spark technique and PUVA therapy. which allowed to increase the clinical effectiveness of treatment.

The indicators were monitored immediately after the course of treatment and after 6-8 months with the evaluation of the results by clinical, visual symptoms, the NAPSI index.

After applying the combined technique, a statistically significant decrease in the areas of structural damage to the nail plates was noted by an average of 76% ($p < 0.01$), in comparison with PUVA therapy and drug therapy by 54.5% ($p < 0.05$) and 9% ($p < 0.01$), which was confirmed by long-term results on NAPSI index values in Psoriatic onychodystrophy patients.

Conclusions: spark discharge causes rhythmic fibrillation of myofibrils and vibration of the tissues of the nail plate with the formation of microshock waves in them, which can improve metabolic, reparative processes, trophic supply, antipruritic and bactericidal effects. In patients who received course treatment of a combined technique in the form of PUVA therapy and Darsonval currents on the nail plates, there was a decrease in the NAPSI index by 76% ($p < 0.01$), against PUVA therapy - by 54.5% ($p < 0.05$) and against standard drug therapy - by 9% ($p < 0.01$)

Keywords: psoriasis, psoriatic onychodystrophy, Puva therapy, D'Arsonval



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High-Dose Pulse Therapy with Hyaluronidase in the Practice of Managing Patients with Compression-Ischemic Syndrome Caused by the Introduction of Stabilized Hyaluronic Acid

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Compression ischemic syndrome (CIS) in the field of injectable cosmetology is a frequent and formidable complication associated with the administration of HA fillers (hyaluronic acid). The pathogenesis of CIS is associated with intravascular administration of HA, as well as obturation of the arteries by the volume of the injected substance. Existing patient management protocols are based on international experience with the high-dose hyaluronidase enzyme. At the moment, there is no consensus, and as a result, clinical recommendations for the use of high-dose enzyme therapy. The purpose of this study is to study the effect of high doses of hyaluronidase, 3-5 times higher than the maximum daily dose of 3000 IU described in the instruction.

The hypothesis of the study is to justify the clinical effectiveness of enzyme therapy at doses exceeding the effective enzyme concentrations necessary to eliminate HA from the lumen of the vessel or tissues.

Laser Doppler flowmetry (LDF) was used as a control method to record blood and lymphatic flow in the vascular microdistrict coinciding with the HA and hyaluronidase injection zone. LDF allows you to detect even minor changes in microcirculation and lymphatic flow. Method sensitivity threshold 0.1 perfusion units.

In the experiment, a complication model was created in laboratory mice by introducing a bolus of HA under the skin of mice, followed by reproducing the natural terms of engraftment of the implant corresponding to the terms of 14-21-35 days.



Hyaluronidase was administered in a pulse regimen with an excess dose of 3-5 times three times, mimicking the course of treatment in CIS. A standard enzyme concentration was used for control, and comparisons were made with intact mice.

A study of the effect of high-dose pulse therapy under the control of LDF revealed statistically significant changes in the blood and lymphatic flow of mice to 2-3 perfusion units compared with the control. The result consisting in intensification of microcirculation under the influence of 3-5 times the enzyme concentrations introduced three times. An experimental model confirms the effectiveness of high-dose pulse therapy.

Continuing the study, we set the goal of justifying the safety of high-dose hyaluronidase administration and detecting tissue changes in laboratory animals.

Keywords: High-dose pulse therapy, hyaluronidase, injectable cosmetology, compression ischemic syndrome (CIS)

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Assessment of Tolerance to Academic Stress in Young People with Various Types of Higher Nervous Activity

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Introduction: In connection with the trend towards personification and individualization of educational trajectories, to increase the effectiveness of the educational process, the study of the relationship between the personal characteristics of medical students and risk factors for the development of asthenic syndrome as a violation of tolerance to academic stress is a topical issue.

Objective: To determine the criteria for the predisposition of young people with different types of higher nervous activity in different periods of the academic load to the development of asthenic syndrome as a violation of tolerance to academic stress based on the study of reactive psychological states and personality characteristics, indicators of cognitive functions.

Materials and methods: The study involved 160 3rd year students of the Medical Institute of Mordovia State University named after N.P. Ogarev, divided into two groups, based on the indicator "Neuroticism", determined by the Eysenck scale: group 1 (n=76) - low level of neuroticism, group 2 (n=84) - high level of neuroticism. All groups were comparable in age composition; the average age in the groups was 20,12±0,19 years. The students underwent a scientific research conducted in three stages under different conditions of the basic academic load and stress level (stage 1 - in the middle of the semester, stage 2 - during the session and stage 3 - after the session). The gender distribution is characterized by the predominance of women in both groups (in group 1 - 43,02% (37) men and 56,98% (49) women, in group 2 - 13,51% (10) men and 86,49% (64) women).

To assess emotional states, we used Spielberger's eight-factor personality questionnaire. To determine the level of asthenia, we used the subjective asthenia rating scale (MFI-20). The obtained data were processed by methods of medical statistics (estimation of the normality of distribution, parametric t-test, non-parametric U-test, χ^2 - to assess the distribution of relative values, r - correlation coefficient; descriptive statistics with the calculation of average values and confidence intervals). Differences were considered significant if the probability of an error-free forecast was more than 95% ($p < 0,05$).

Results: We studied the dependence of indicators of asthenia on the type of higher nervous activity (HNA) in young people at the third stage of the research after a period of intense intellectual workload and a high level of stress. In all groups, we registered average indicators of asthenia, exceeding the reference values of the physiological norm. The determination of the total percentage of asthenia showed its maximum value in group 2 (51.78±5.42), which indicates the presence of severe asthenia, and the minimum in group 1 (38.68±3.98), which indicates the presence of moderate asthenia. It should be noted that group 1 was characterized by a low level of neuroticism, which probably increases the student's stress resistance during high intellectual loads and reduces the likelihood of developing asthenia.



The study of the indicator of reduced activity revealed that its maximum value was determined in group 2 (14,37±1,66), and the minimum in group 1 (12,22±1,64). Determining the indicator of reduced motivation showed that its maximum value is observed in group 2 (12,25±1,32), and the minimum in group 1 (10,90±1,57).

Evaluation of the indicator of physical asthenia revealed the following patterns: its maximum value is observed in group 2 (13,80±1,50), and the minimum in group 1 (10,95±1,53). The study of the indicator of mental asthenia showed that its maximum value is observed in group 2 (12,23±1,51), and the minimum in group 1 (10,60±1,48).

Thus, the greatest severity of asthenia was observed in respondents with a high level of neuroticism (group 2), and the least - in individuals with a low level of neuroticism (group 1).

The study of the indicators of emotional balance revealed the conjugation of the dynamics of the indicators of the latter in different periods of intellectual load with the characteristics of the HNA of young people. When assessing the reactive states of respondents, such as interest, aggression, anxiety and depression at different stages of the study with different levels of load, the following patterns were identified: at the first stage of the study, respondents in group 1 (with a low level of neuroticism) showed a higher level of interest than group 2 (with a high level of neuroticism), lower levels of aggression, anxiety and depression. Dynamic changes in these indicators after an intense intellectual load during the session compared to the middle of the semester are characterized by a decrease in all the studied indicators in the group 1 and their increase in the group 2.

Evaluation of individual personality characteristics, such as curiosity, aggressiveness, anxiety and depression, revealed generally similar patterns in the dynamics of these indicators and their differences between groups, as well as similar reactive states.

The study of the volume of short-term memory did not reveal significant differences between groups and dependence on the type of higher nervous activity at stage 1 (in the middle of the semester with a basic level of academic load). The average value of short-term memory in all groups ranged from 86,31±2,13% to 89,06±1,97% of the amount of information provided

At the second stage of the study, during the period of intense intellectual load (session), significant differences were revealed in the indicators of the volume of short-term memory - the largest value was determined in group 1 (81,23%), and the smallest indicator - in group 2 (78,09%).

Conclusions: 1. The research established a direct relationship between indicators of asthenia and the level of neuroticism in young people; in females, asthenia occurs significantly more often.

2. Persons with a high level of neuroticism in the period after an intensive study load and a high level of academic stress have pronounced asthenia and tension in the mechanisms of psychosocial adaptation.

3. Persons with a high level of neuroticism are the least resistant to stress, this is reflected in the change in cognitive functions in a decrease in the indicator of short-term memory during a period of stress.

Keywords: Educational process, personification of learning, higher nervous activity, asthenic syndrome, autonomic regulation, risk factors, stress tolerance, academic stress.

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Genetic Determinants of Antiretroviral Drug Resistance in Hiv Therapy

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Over the period since the first description of cases of acquired immunodeficiency syndrome (AIDS) in 1981, the infection caused by the human immunodeficiency virus (HIV) has evolved into a pandemic, erasing geographical, national, and social boundaries.

It is important to note that in recent years, HIV infection has extended beyond vulnerable population groups in the Russian Federation. It is actively spreading through sexual contact within the general population.

HIV-1 is the most genetically diverse virus, and its high genetic variability is a result of molecular variability. During virus replication, numerous genetic errors occur, along with high mutation rates and genetic material recombination. This leads to the emergence of different variants of HIV-1, known as genotypes and subtypes.

The genetic diversity of HIV-1 can influence the speed of disease progression and the effectiveness of treatment. Some genotypes may be more aggressive and rapidly progressive, which can lead to faster development of AIDS. Additionally, genetic variations in HIV-1 can affect the efficacy of antiretroviral drugs, leading to the development of drug resistance.

Studying the genetic diversity of HIV-1 is crucial for developing effective treatment strategies and preventive measures. It helps identify the most prevalent genotypes and subtypes in specific regions and detect mutations associated with drug resistance. This aids in selecting appropriate antiretroviral drugs and personalizing treatment for each patient.

Antiretroviral therapy (ART) drug resistance is associated with the high mutational activity of HIV and is one of the reasons for treatment inefficacy and disease progression. One of the main indicators of treatment effectiveness is the analysis of viral load (VL), which becomes undetectable in the case of successful therapy.

The research objective is to investigate the causes of virological treatment failure in ART and conduct an analysis of the prevalence of ART drug resistance mutations among HIV-infected patients residing in the Republic of Mordovia and receiving ART.

Materials and Methods: 37 blood samples with detectable viral load were collected from HIV-infected patients under follow-up at the "Mordovian Republican Center for Prevention and Control of AIDS" who had been on antiretroviral therapy (ART) for more than 24 weeks. Epidemiological, demographic, and clinical data, including the experience of ART usage for HIV therapy, were obtained from the patients' medical records. Drug resistance testing of HIV was conducted using genotypic methods.

In this study, 37 blood samples were obtained from HIV-infected patients with detectable viral load who were under follow-up at the "Mordovian Republican Center for Prevention and Control of AIDS." All patients had been receiving ART for more than 24 weeks.



Epidemiological, demographic, and clinical data, including information on the use of ART for HIV therapy, were collected from the patients' medical records.

Genotypic testing was performed to assess drug resistance in HIV. This method allows for the detection of mutations in HIV genes that may be associated with drug resistance. Analyzing HIV genotypes helps determine which antiretroviral drugs may be effective or ineffective against specific HIV strains.

Thus, the study utilized blood samples, clinical data, and genotypic testing to investigate the prevalence of drug resistance mutations among HIV-infected patients in the Republic of Mordovia.

Results: The study included patients with varying numbers of previously prescribed therapy regimens. Only one ART regimen was received by 8.1% of the patients in the study group (3 individuals), two regimens were used in 40.5% of cases (15 patients), three regimens in 18.9% (7 patients), four regimens in 5.5% (2 individuals), and more than five regimens were used in 27% of patients (10 individuals).

Analysis of the ART treatment revealed that a significant portion of the surveyed patients, based on the analysis of outpatient records, had received more than one ART regimen. (Quite frequently, we observed changes in the therapy regimen over the course of patient follow-up).

In terms of adherence within the study group, it was found that 72.9% of patients demonstrated high adherence, while 21.6% reported occasional missed doses and had moderate adherence. Only 5.5% acknowledged having low adherence.

The study group of patients showed virologic progression within 24 weeks of ART initiation, which led to a change in the ART regimen.

Resistance to only one class of antiretroviral drugs was detected in 13.3% of patients with resistance. Resistance to two classes (NRTIs - nucleoside reverse transcriptase inhibitors and NNRTIs - non-nucleoside reverse transcriptase inhibitors) was observed in 80.0% of cases. Resistance to three classes was found in 6.7% of patients. Samples with resistance isolated to either NRTIs or NNRTIs were not encountered; resistance to protease inhibitors (PIs) was observed in 13.3% of patients.

In samples with pharmacoresistance to integrase inhibitors (nucleotide inhibitors), the most frequently encountered mutations were LL3F (38.4%), M46I (11.2%), and L89T (9.3%).

Resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) was caused by the following mutations:

- M184V (81.1%) - resistance to lamivudine and emtricitabine;
- A62V (38.5%) and T215F (19.3%) - analogs of thymidine;
- L74V (18.1%) - non-thymidine analogs of nucleosides;
- K103N (36.4%) - non-nucleoside inhibitors.

These mutations are the major determinants of drug resistance in HIV-1 to the respective classes of antiretroviral drugs.

Conclusions: In the Republic of Mordovia, among HIV-infected individuals, pharmacoresistance to antiretroviral therapy (ART) was associated with mutations in HIV genes in 87.5% of cases. Considering the high prevalence of drug resistance mutations in patients with virologically ineffective ART, it is necessary to monitor HIV drug resistance.



The lack of drug resistance monitoring can lead to the spread of primary drug-resistant strains of HIV, increased difficulty in the primary diagnosis of the disease due to changes in the clinical course of HIV infection, increased complexity in managing these patients, and consequently, a worsening of the epidemiological situation.

Keywords: HIV-1, GENETIC DETERMINANTS, Antiretroviral therapy, pharmacoresistance, mutations, genetic diversity

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The Importance of Routine Laboratory Parameters for Early Prediction of Covid-19 in Patients of Different Sexes

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Relevance: The COVID-19 pandemic is officially over. This decision was made by WHO on May 5, 2023. In three years, the coronavirus has claimed the lives of at least 20 million people. Compared to 2021, the situation around the disease is significantly better. However, the study of markers associated with an unfavourable outcome is still relevant, as the circulation of COVID-19 continues. The purpose of our work is to study the correlation of dynamic changes in laboratory markers with the outcome of COVID-19 disease in people of different sexes, to identify the most significant criteria for the development of a prediction algorithm, and to determine the expediency and accessibility of certain laboratory tests.

Materials and methods: For analysis, the case histories of patients with COVID-19 (n=92), who were treated at the (S.V. Katkov Republican Clinical Hospital in Saransk) were randomly selected. All patients were divided into two groups by gender. Each group was further divided by the outcome – recovery: men (n=29), women (n=46), death: men (n=8), women (n=9). Student's t-test, Mann Whitney's U-test, chi-square test and correlation analysis (SPSS Statistics 13) were used for statistical analysis. The diagnosis of COVID-19 was confirmed by collecting throat swab samples for PCR SARS-CoV-2 test. The age of the patients ranged from 36 to 90 years, with an average of 69 years. Descriptive statistics were used to generalise the characteristics of the studied population.

Results: After analysing complete blood count indicators, the most significant parameters for predicting the outcome of the disease were identified. It was found that at admission, the average haemoglobin values in men with an unfavourable outcome were lower by 14.2%, haematocrit – by 14.5%, RBC – by 13%; in women, haemoglobin values were lower by 25.1%, haematocrit – by 21.4%, RBC – by 22.2% compared to those who recovered (p < 0.001). In dynamics of changes, haemoglobin indicators in men with an unfavourable outcome were 23% lower, haematocrit – 18.4%, RBC – 21%; in women, haemoglobin levels were lower by 9.9%, haematocrit – by 9.9%, RBC – by 15.9% compared to those who recovered (p < 0.001). Also, according to the results, at admission, leukocytosis was detected in patients with an unfavourable outcome due to neutrophilia, the indicators of those who recovered were normal. In dynamics of changes in patients with a favourable outcome, an increase of WBC levels was detected, as opposed to the patients with unfavourable outcome, who developed lymphopenia. At admission and in dynamics, ESR indicators in men with an unfavourable outcome were higher by 28.4 and 96.3%, in women – by 59.5 and 36.9% respectively, compared to those who recovered (p < 0.001). When assessing the haemostasis system in women, there were differences in indicators depending on the outcome of the disease: PTI at admission and in dynamics in patients with an unfavourable outcome is lower by 9.4 and 29.8% respectively, compared with those who recovered (p < 0.001). At admission, INR



indicators were lower in patients with an unfavourable outcome by 17.9%. The dynamics revealed a multidirectional change in values: in patients with a favourable outcome – a decrease from 1.7 to 1.2, with an unfavourable outcome – an increase from 1.4 to 1.6, considering the anticoagulant therapy. According to the results of urine test, at admission and in the dynamics of patients with an unfavourable outcome, regardless of gender, an increase in WBC levels was detected. Despite the fact that in all clinical guidelines high CRP level is an important indicator of the progression and the outcome of the disease, we did not find a statistically significant difference in the dynamics of these groups of patients in our retrospective analysis.

Conclusions: At admission, the groups with favourable and unfavourable outcomes, regardless of gender, differed in terms of red blood parameters, WBC and ESR levels. Lymphopenia is present in both groups with an unfavourable outcome, and it is associated with the progression of the disease. ($p < 0,001$). A more distinct increase in WBC levels was observed in both groups with an unfavourable outcome. In women, depending on the outcome of the disease, differences in coagulogram parameters were detected.

The most significant markers for assessing the prognosis of the disease in the early stages in both sexes are the parameters of red blood, the dynamics of changes in the number of lymphocytes, leukocytes in the the complete blood count; in women – coagulogram parameters.

Keywords: COVID-19, laboratory parameters, comparative characteristics.

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Anti-Tumor Activity of Estrogen and Colchicine in Brain Tumor Models in Vitro

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Introduction: Malignant tumors are one of the leading diseases in the world, causing about 10 million deaths per year (Dhyani P. et al., 2022). Sex hormones can have an anti-inflammatory effect on the brain, as well as influence the pathogenesis and outcome of tumors, including ependymoma and glioblastoma (Hirtz A. et al., 2020). Tumors, including ependymomas, are more common in men than in women, respond less well to treatment, and the toxic effects of therapy are more pronounced. The incidence of ependymomas in children reaches 30%, in adults - up to 3%. The peak incidence of brain tumors in children occurs at an early age - up to 4 years, when circulating sex hormones are at a low level (Sun T. et al., 2015). In postmenopausal women, the frequency of ependymoma and other brain tumors increases and also negatively correlates with the level of sex hormones (Muskens Ivo S et al., 2019). With glioblastoma, it has been shown that a higher survival rate is observed in the Asian population, so survival to two years is 50% in it, versus 40% in Europeans (Leece R. et al., 2017; Ostrom Q.T. et al., 2018). It is known that one of the main food sources of Asian peoples are plants of the legume family, which contain phytoestrogens (Yildiz F., 2005). Plant metabolites such as alkaloids and steroids can be used to prevent as well as treat tumors. They change the diversity and composition of the intestinal microflora (Clavel T. et al., 2005). The plant alkaloid colchicine is an antimetabolic drug that binds tubulin and blocks the polarization of microtubules, forming a tubulin-alkaloid complex, inhibits cell ion channels, migration and metastatic potential of tumor cells, which leads to their death. Does not cause cross-resistance to DNA alkylating drugs, has an anti-inflammatory effect (Dalbeth N. et al., 2014). The phytoestrogen genistein present in soy is a known inhibitor of DNA methyltransferase, histone deacetylase, histone H3 and can induce the activity of histone acetyltransferases, which are involved in the epigenetic regulation of the cell genome (Tuli H.S. et al., 2023), which may affect its antitumor activity. However, data on the role of sex hormones in the processes of oncogenesis in the CNS is not enough. Further research is needed on the effects of estrogens and plant alkaloids on the development of brain tumors. The aim of the study was to evaluate the cytotoxic activity of estrogen and colchicine on neonatal rat brain cells and in vitro ependymoma tissue - rat ependymoma tumoroids and on adherent cell lines of mouse ependymoma EPNT-5, malignant glioma 9L and RG2 of rats.

Materials and methods: The study was performed on an adhesive cell culture of the brain of a newborn rat (2D model) and ependymomas: tumoroids strain 14-60-1, 14-60-4, 14-4-4 (3D model), adhesive cell lines EPNT-5 (2D model), 9L and RG2 in vitro. Cells were cultured in IMDM glutamax medium (Gibco, USA) with 10% fetal calf serum (Hyclone, USA), 0.1 mg/ml antibiotic



penicillin and streptomycin (Gibco, USA) at $t=37.0\text{ C}$, in 5% carbon dioxide atmosphere in 6 well plates (SPL Lifesciences, South Korea). Synthetic progestin - hexestrol diacetate, a non-steroidal estrogen from the stilbestrol group, an ester that has been used for estrogen replacement therapy and in the treatment of certain hormone-dependent types of tumors. The antitumor activity of estrogen and colchicine was assessed by the morphological characteristics of tumor models and by the MTT test. Observation groups: 1) Intact. 2) Estrogen - 0.1 mg / ml. 3) Estrogen - 0.0001 mg / ml. 4) Colchicine - 0.0002 mg / ml.

The results were taken into account 24-72 hours after the addition of drugs. Results and discussion. Estrogen and colchicine exerted an antitumor effect on all studied ependymoma models and malignant gliomas. Both drugs were also cytotoxic to neonatal rat brain cells. Intact brain cells of a newborn rat, EPNT-5, 9L, and RG2 were attached to the substrate, the cells had numerous processes and proliferated during all periods of observation, tumoroids 14-60-1, 14-60-4, 14-4-4 attached to the substrate, individual cells actively defiled from the spheres. At 24 and 72 hours after the addition of both colchicine and estrogen to all cell cultures and tumoroids, cell proliferation was inhibited, spheroids and cells detached from the substrate, spheres disintegrated into individual cells that were not fixed at the bottom of the wells, the effects were more pronounced after 72 hours of observation. MTT analysis in cell models showed a decrease in metabolic activity and cytotoxicity of estrogen and colchicine. The effects of estrogen were similar at different doses, both 0.1 mg/ml and 0.0001 mg/ml. Estrogens modulate three main features of tumors - proliferation, migration/invasion and survival (Hirtz A. et al., 2020). Further research is needed on the effects of estrogens and plant alkaloids on the development of brain tumors.

Conclusions: A pronounced antitumor effect of both estrogen and colchicine was noted on in vitro ependymoma tissue models: rat strain 14-60-1, 14-60-4, 14-4-4 and mouse ependymoma cell lines EPNT-5, malignant gliomas 9L and RG2 rats. Estrogen also had a cytotoxic effect on neonatal rat brain cells.

Keywords: Ependymoma, malignant glioma, colchicine, estrogen, tumoroids, in vitro antitumor activity

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Extracellular Matrix Remodeling the Upper Respiratory Tract in Bronchial Asthma

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From 80 to 100% of patients with atopic bronchial asthma have allergic rhinitis, which indicates the need to pay close attention to the state of the upper respiratory tract in them [1]. Modern studies demonstrate that inflammatory processes in the mucous membrane of the upper and lower respiratory tract in patients with asthma are identical and are most often associated with a Th2-dependent mechanism [2].

If we assume that the result of inflammation is remodeling, then one would expect clear structural changes in patients with bronchial asthma in the upper respiratory tract as well due to the persistence of inflammation caused by allergic rhinitis. However, modern studies are quite contradictory and more often indicate that, in general, remodeling is not a characteristic feature of this disease [3].

In the study of biopsy samples of the nasal mucosa, both in seasonal and year-round course of allergic rhinitis, an increase in the total thickness of the basement membrane was demonstrated compared to the value in healthy people in the first hours after exposure to causally significant allergens. However, 24 h after exposure, despite the influx of eosinophils, there was no further increase in basement membrane thickening [4, 5]. Apparently, remodeling in the upper airways is not a key feature of the immunopathogenesis of allergic rhinitis in patients with bronchial asthma. However, it should be noted that according to the results of our studies, isolated allergic rhinitis occurs only in a part of children with bronchial asthma. In the majority, we found its combination with other variants of the pathology of the upper respiratory tract, including abnormalities in the development of intranasal structures, hypertrophy of the pharyngeal tonsil, and in some adolescent patients, hypertrophic changes in the nasal mucosa were detected, which we regarded as a possible debut of polyposis rhinosinusitis [6, 7].

It is known that chronic rhinosinusitis and bronchial asthma have a close relationship, especially in the adult cohort of patients [8, 9]. Chronic rhinosinusitis is a broad term that includes a group of heterogeneous inflammatory diseases and is subdivided into chronic rhinosinusitis with and without nasal polyps [10]. Up to 14% of patients with chronic rhinosinusitis with polyps and patients with aspirin-induced respiratory diseases demonstrate severe asthma [9, 11].

Unlike allergic rhinitis, tissue remodeling is a hallmark of chronic rhinosinusitis. In chronic rhinosinusitis with polyps, destruction of epithelial cells in the nasal mucosa is observed, and the presence of excess mucus can be explained by hyperplasia of the mucous glands and hypersecretion of mucin [12, 13]. Basement membrane thickening shows an association with the



severity and duration of the disease, as well as with the presence of asthma, and, apparently, does not depend on the degree of eosinophilic inflammation [14, 15].

Degradation of the extracellular matrix is a key pathological link in chronic rhinosinusitis with polyps, while there is a change in the architectonics of tissues, their growth, and the formation of pseudocysts.

Currently, descriptive studies do not yet provide a detailed understanding of the possible mechanisms of remodeling in patients with chronic rhinosinusitis [3]. Thus, allergic rhinitis does not appear to be characterized by remodeling processes in the mucosa, with the exception of some thickening of the basement membrane. In chronic rhinosinusitis with polyps and in bronchial asthma, epithelial cell damage is observed along with goblet cell hyperplasia. In both cases, activation of the epithelial-mesenchymal-trophic unit was noted. Perhaps this mechanism lies in the initial epithelial vulnerability leading to active submucosal mesenchymal activation. As for the submucosa, similar remodeling processes in chronic rhinosinusitis with polyps and in allergic bronchial asthma include hypertrophy of the mucous glands and excessive production of extracellular matrix components. However, there are significant differences: pseudocysts are observed only in the nasal mucosa and paranasal sinuses in patients with chronic rhinosinusitis with polyps, but not in the mucous membrane of the lower respiratory tract in bronchial asthma [3].

Further research aimed at studying the processes of remodeling of the upper and lower airways in patients with bronchial asthma and comorbidities of the upper respiratory tract is necessary to clarify the main mechanisms and develop more effective therapeutic strategies for the treatment of allergic diseases and correct the clinical consequences of airway remodeling.

Keywords: Extracellular matrix, bronchial asthma, allergic rhinitis; chronic rhinosinusitis

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Mast Cells in the Microenvironment of Uveal Melanoma

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Background: Uveal melanoma (UM) is a malignant tumor of neuroectodermal origin, often found in people of working age and prone to early metastasis [1–4]. In the Russian Federation, the incidence of UM varies from 6.2 to 8 new cases per 1,000,000 population per year [1]. Among the various areas of research in fundamental oncology in the last two decades great attention is paid to the study of the microenvironment (MO) tumors [5–8]. According to domestic and foreign scientists [5, 6], the MO takes an active part in vital activity of the tumor, ensuring the growth, proliferation and migration of malignant cells. Majority developments [7, 8] in the field of tumor MO targeting is in the early stages, however, new trends in changing the paradigm of anticancer treatment with the obligatory inclusion of drugs that affect not only the tumor itself, but also the cells of the MC, are beginning to become increasingly important.

Purpose. To study the morphological features of the microenvironment of a tumor nodule in the eyes with uveal melanoma, focusing on mast cells.

Material and methods: A total of 43 enucleated eyes with uveal melanoma (260 histological specimens) were examined. The patients' age averaged 54±2.7 years. The morphopathological types of tumors were as follows: epithelioid-cell (n=9; 20.9%), spindle-cell type AB (n=15; 34.9%), and mixed-cell (n=19; 44.2%). The tumor prominence was 4.7±1.3 mm; the base diameter was 13.5±3.3 mm. Statistical methods, such as Microsoft Excel, Statistica 10.1, Spearman's rank correlation coefficient (rs), were applied.

Results: Mast cells in the microenvironment of uveal melanoma were present in 18 (41.9%) of the 43 eyes. There was a significantly higher correlation between the mixed-cell type of tumor and the accumulation of mast cells (rs =0.636). The correlation coefficient (rs) of the number of mast cells with the degree of tumor pigmentation in terms of densely and weakly pigmented forms was 0.571 and 0.717, respectively. Tumor invasion through the sclera was detected in 7 (16.3%) eyes with mast cells (rs =0.395). Tumor growth in the emissarium in the presence of mast cells was determined in 8 (18.6%) cases (rs =0.469). Comparison established a correlation between the number of mast cells and the sections of tumor blood vessels (rs =0.21). Granulated cells were noted in 15 (34.9%) cases; degranulated ones were seen in 3 (7%) cases of the 43 examined eyes. with an ejection of granules around the tumor cells, which may be evidence of their interaction. Granules were ascertained to be released around the tumor cells, which may be suggestive of their interaction.

Conclusion: The study of the mast cell population as one of the components of the tumor microenvironment can be used to elaborate novel approaches for the targeted treatment of uveal melanoma, in particular for its impact on tumor angiogenesis, by using mast cell inhibitors. Therefore, it is relevant and promising to conduct further investigation of mast cells in uveal melanoma.

Keywords: mast cells, microenvironment, uveal melanoma



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Adaptive Changes of the Antioxidant System in Oncogynecological Patients with Additional Therapy

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The intensification of free radical oxidation plays an important role in the mechanisms of development of many diseases, including malignant growth. Reactive oxygen species are considered, on the one hand, as carcinogenesis initiators and the most important factors in cancer progression [1,2,3], on the other hand, as agents that promote the elimination of cancer cells in cancer therapy [4]. More intensive peroxidation of lipids (LPO) and proteins, accompanied by a violation of antioxidant protection, was demonstrated in the progression of various cancers [1,4,5], including studies on gynecological cancers conducted at the National Medical Research Centre for Oncology: ovarian cancer (OC) depending on its prevalence and severity [6]; cervical cancer (CC) [7,8]; vulvar cancer [9]. An abnormal antioxidant status is associated with the development of oxidative stress [10].



The use of cell technologies as an immunological component of treatment can help overcome tumor resistance to chemotherapy (CT) and improve the effectiveness of treatment of patients; that is why more than 60 dendritic cell vaccines (DCV) against cancer have been created in cancer centers around the world. The successful use of xenon for treatment and rehabilitation in various fields of medicine, management of stress-induced disorders in people with dangerous professions and participants in military conflicts and emergencies, determines its relevance in oncology to improve the quality of life in hormone-reducing surgeries.

The purpose of this study was to analyze the effects of some influences increasing the adaptive capabilities of the body on the blood redox status of patients with gynecological cancers.

We analyzed the dynamics of changes in the main antioxidant enzymes in the blood of CC patients with the inclusion of DCV or xenon therapy in the immunotherapy regimen, as well as in patients with OC with perioperative Remaxol. The effect of vaccine therapy was studied in 22 patients with CC aged 27-65 years, divided into 2 groups: 12 patients with newly diagnosed advanced CC St IIIB-IVB who underwent primary chemoradiotherapy in combination with DCV, and 10 patients with progressive cervical cancer St IIB-IIIIB who received cycles of second-line chemotherapy in combination with DCV. DCV containing at least 98% of living mature dendritic cells obtained from mononuclear cells by differentiation using the cytokines GM-CSF, IL-4, and TNF- α followed by loading with tumor antigens was administered intradermally once a week at a dose of 10 million cells (up to 12 cycles accompanying CT courses). The effect of xenon therapy was analyzed in 60 patients of reproductive age (up to 45 years) with CC T1A2B2N0M0 with the manifestation of post-castration syndrome after uterine extirpation with appendages; 32 patients received xenon, and 28 patients did not receive it. Xenon therapy was carried out on days 4-8 of the postoperative period by supplying a xenon-oxygen mixture through a face mask using a therapeutic circuit with gas flow control. Remaxol, a complex of physiologically active components: succinic acid, methionine, inosine and nicotinamide, was included in the anesthetic management of the surgery for 36 OC patients aged 55.6 \pm 10.3 years. Remaxol 400 ml was administered before and during the surgery and 800 ml in the next three days. The activity of superoxide dismutase (SOD), catalase (CA) and glutathione peroxidase (GPO), the level of reduced glutathione (RG), as well as the content of LPO products, malondialdehyde (MDA) and diene conjugates (DC), were studied by spectrophotometric methods in all patients with gynecological cancers. The same biochemical parameters were studied in 30 women of comparison groups without cancer of comparable age (25–65 years).

Patients with CC were characterized by LPO intensification confirmed by an increase in MDA levels and a multiple increase in DC, together with a disturbed ratio of antioxidant enzymes, as well as almost doubled levels of MDA in erythrocytes and blood plasma after chemotherapy cycles. Multicourse DCV allowed maintaining the oxidative status of the blood at an optimal level, which normalized LPO. At the same time, vaccine therapy led to an increase in the activity of the glutathione system, which became the most important component of antioxidant protection in the blood of patients with advanced and progressive forms of CC. The most pronounced response to the inclusion of DCV, which led to complete or partial regression of the tumor in 83% of cases, was observed in primary patients with stage IIIB-IV CC; stabilization was registered in 60% of cases with recurrent CC tumors.



The inclusion of xenon therapy in the postoperative treatment for CC downregulated the levels of MDA and DC as a result of the activation of SOD and CA. There was also an increase in the level of RG involved in the detoxification of hydrogen peroxide and lipid peroxides. A relief in pain and psycho-somatic symptoms was noted, indicating the normalization of the homeostasis systems.

The use of Remaxol as part of multimodal anesthesia improved the quality of anesthetic management, helped to reduce the levels of LPO products in the blood of patients with OC, prevented the development of hepatopathy and endogenous intoxication, facilitating the development of long-term adaptive mechanisms in the immediate perioperative period in patients with OC. The initially two-fold reduced ratio of SOD and CA characterizing the disruption of the first line of antioxidant protection observed in OC was normalized in patients receiving Remaxol due to a more pronounced activation of SOD.

The anti-stress effect of xenon therapy and the inclusion of Remaxol for the metabolic correction of anesthesia were confirmed in the study of adaptational reactions. Determination of the adaptive status of patients showed that the inclusion of xenon therapy led to the dominance of anti-stress reactions in CC patients, while in patients without it, the stress reaction prevailed in the postoperative period. In patients with OC, Remaxol also decreased the frequency of stress reactions and helped to form the most favorable anti-stress reaction of calm activation.

Thus, the use of various variants of accompanying therapy with the mechanism of action which presumably involve an increase in the adaptational capabilities of patients with gynecological cancers demonstrates a similar picture of the normalization of the blood redox status.

Keywords: Cervical cancer, ovarian cancer, antioxidant blood system, lipid peroxidation, dendritic cell vaccine, xenon therapy, remaxol

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Evaluation of Heart Rate Variability in Individuals with Different Adaptation Reserves of the Cardiovascular System

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Introduction: According to the World Health Organization, diseases of the cardiovascular system (CVS) have been the leading cause of death worldwide for 20 years [1]. Unfortunately, there are currently no effective treatments for chronic cardiovascular disease (CVD). However, the analysis of heart rate variability (HRV), being one of the most informative and non-invasive diagnostic methods [2], will make it possible to diagnose CVD early and prevent severe complications, which contributes to maintaining the health of young people.

The research purpose is assess HRV in individuals with different adaptation reserves of the cardiovascular system.

Materials and methods: The study included 257 volunteers aged 19-27 years, who were divided into 3 groups depending on the value of the adaptive potential (AP), calculated by the formula R.M. Baevsky [3]. Group 1 (n=148) consisted of young people with satisfactory adaptation ($AP \leq 2.6$); the 2nd group (n=72) – with tension of adaptation mechanisms ($2.6 < AP \leq 0.05$). Body weight in the 1st group averaged 59.7 ± 0.07 kg, which is 17.3% and 32.3% less than in the 2nd and 3rd groups, respectively ($p < 0.001$). BMI in the 1st and 2nd groups corresponded to normal values, in the 3rd group the BMI value corresponds to preobesity and exceeds the values of this indicator in the first two groups by 27.7% and 16.7%, respectively ($p < 0.001$). SBP in the 1st group was 115 ± 0.069 mm. rt. Art., which is 10.15% and 20.8% less than in the 2nd and 3rd groups, respectively ($p < 0.001$), while in the 3rd group the mean SBP was 145.21 ± 0.34 mm. rt. Art., which corresponds to the 1st degree of arterial hypertension. Mean DBP was within normal limits in all groups. On average, in the 1st group, the heart rate was 79.18 ± 0.07 bpm, which corresponds to normal values, in the 2nd and 3rd groups - 90.98 ± 0.2 and 95.37 ± 0.42 bpm respectively. In a comparative aspect, the value of this indicator is higher in the 3rd group by 20.44% and 4.82% than in the 1st and 2nd



groups, respectively ($p < 0.001$). According to the IC data, in the 1st and 3rd groups, persons with a normal balance of the autonomic nervous system prevailed, where they accounted for 43.2% and 48.6%, respectively, and in the 2nd group, sympathetic influences prevailed in most respondents. in the regulation of CVS (48.6%).

The arithmetic mean of the duration of NN intervals in the epoch of analysis (RRNN) in the 1st group averaged 779.4 ± 1.004 ms, which is 7.32% and 14.18% more than in the 2nd and 3rd groups, respectively ($p < 0.001$). The root-mean-square value of consecutive differences (RMSSD) in the 1st group averaged 120.7 ± 1.1 ms. and it was also more than in the 2nd and 3rd groups by 93.12% and 323.5%, respectively ($p < 0.001$). Number of pairs of consecutive NNs that differ by more than 50 ms. (NN50) averaged 142.1 ± 1.2 in group 1, 64.2 ± 0.9 and 36.6 ± 1.5 in groups 2 and 3, respectively. ABI in the 1st group averaged 53.2 ± 0.25 , in the 2nd group - 62.2 ± 0.34 , in the 3rd group - 76.8 ± 0.8 . In a comparative aspect, the value of this indicator in the 1st group is 14.45% less than in the 2nd ($p < 0.001$), and 30.7% less than in the 3rd group ($p < 0.001$). The average value of ARI in the 2nd group was 2.04 ± 0.008 , which is 9.9% less than in the 1st ($p < 0.001$), in the 3rd group the value of this indicator was 2.28 ± 0.02 , however, the differences between the 2nd and 3rd groups are not statistically significant. SI in the 1st group was 62.5 ± 1.57 , in the 2nd and 3rd groups - 45.3 ± 0.3 and 60.3 ± 0.9 , respectively. In a comparative aspect, the value of this indicator is 38.01% higher in the 1st group than in the 2nd ($p < 0.001$), the differences between the 1st and 3rd groups are not statistically significant. ARPI was also higher in the 1st group by 176% and 123% than in the 2nd and 3rd groups, respectively ($p < 0.001$).

Against the background of respiratory modulation, the RRNN value decreased in all groups: in the 1st group by 0.43% ($p < 0.01$), in the 2nd group by 0.23%, in the 3rd group by 0.26%. In the last two groups, the differences before and after hyperventilation were not statistically significant. The RMSSD value increased in the 1st group by 36.6% ($p < 0.001$), in the 2nd group - by 140.1% ($p < 0.001$), in the 3rd group - by 272.7% ($p < 0.001$). The values of the NN50 indicator in the 1st group decreased by 58.4% ($p < 0.001$), in the 2nd group - by 20.3% ($p < 0.001$), and in the 3rd group increased by 13.9% ($p < 0.001$). In the 1st group, the values of ABI, PAPR and SI decreased by 33.28%, 39.9% and 12.9%, respectively ($p < 0.001$), while the value of ARI, on the contrary, increased by 28.2% ($p < 0.001$). In the 2nd ABI decreased by 22.23%, ARI, ARPI and SI increased by 44.4%, 9.13% and 19.02%, respectively ($p < 0.001$). In the 3rd group, ABI, ARPI and SI decreased by 26.7%, 22.2% and 21.2%, respectively, ARI increased by 4.2% ($p < 0.001$).

Conclusions: The study has shown that a decrease in HRV is associated with a decrease in the adaptive capacity of the cardiovascular system. The value of RRNN, RMSSD, NN50 indicators and calculated indices correlates with the level of SBP, DBP and BMI (the most significant CVS disease risk factor for young persons). Respiratory modulation led to an increase in HRV in young people; under violation of CVS adaptation, these changes were lesser than at norm.

Keywords: Cardiovascular disease, heart rate variability, formula R.M. Baevsky

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The Living Dialectics of the Common Non-Specific Adaptation Reactions System as a Theoretical Basis of the Physiological and Pathological Approaches of the Translational Medicine

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Relevance: At the current stage, there has been progressing a global advancement of high-technology methods of diagnostics and treatment based on exceptionally science-intensive molecular-genetic, electronic, wave, quantum, robotized approaches of a higher life quality and health care. Despite the uniqueness of development of medical technologies aimed at the human body, it is difficult to achieve a managed process of the steady recovery if the regularities of its response are not known. And practice, in this sense, is ahead of theory in terms of translation of a product into the clinical environment, and proposes a specific mechanism of exposure of the body at best.

The purpose is to move the adaptational reactions theory on as a necessary tool of the translational medicine of high technologies for a managed increase of efficiency of treatment, for a higher life quality and life span.

Methodology and methods: Stress theory and discovery of the anti-stress reactions. Principles and technologies of the activation therapy.

Results of the retrospective studies: The “exposure quality” category had always prevailed in medicine. The role of the quantity was first noticed in the 1940s by Hans Selye, a young Canadian physician. Having overcome the psychological barrier of primacy of the quality and specificity in the body’s response to a stimulus, Hans Selye, enthusiastic about non-specificity, focused on proving an almost unbelievable fact which is stereotypical response of the body to strong, high stimuli, different in quality. Selye’s genius is in having first linked, with a single axis, the hypothalamus-pituitary-adrenalin and thymus-lymph CASCADE of changes in the entire body, and having understood that defense would be achieved at the high cost of damages and big energy waste (1). The body’s resistance decreases in acute stress, while in chronic stress it becomes extremely low. And this is a non-specific background for any kind of pathology, including cancer (2).

However, Hans Selye understood the ambiguity of stress (S) and introduced later the concepts of good “eustress” and bad “distress”, which blur the boundaries of the classical concept.



Given that besides the strong exposures there are also relatively weak and “medium”, moderate stimuli, the relationship between the discrete value of stimulus and the entire body’s response has been studied in detail. These fundamental researches were first carried out at the Experimental Department of the Rostov Research Institute of Oncology (now National Medical Research Centre for Oncology) by Lubov Garkavi, Maria Ukolova and Elena Kvakina, the authors of the Discovery n.158 (1975) of the before unknown regularity of the body’s response depending on intensity of stimulus, and not on its quality (3). It is them who have the priority and proof of existence of different evolutionarily developed archetypes of reactions alternative to stress. “In the hands of scientists – as J.W.Goethe wrote – there are often parts, but very seldom there is the sacred connecting thread”. The Russian scientists have found that thread and have linked together the understandings of the quality and quantity regularities of the body’s response.

Since the first hours, exposing to a weak stimulus (a weak electric stimulation of hypothalamus or an administration of small doses of neurotropic substances, a contactless exposure of the hypothalamus area to an alternating electromagnetic field, an oral administration of small doses of plant- and animal-based biostimulants) evolved, regardless of the stimulus quality, a stereotypical common non-specific adaptational reaction of the body, named training reaction, with an anti-stress nature of changes. The mechanism of the restrained progressive increase of non-specific resistance was completely discovered, and the pattern of the symptom complex of changes in the CNS, hypothalamus-pituitary, endocrine, and thymus-lymph systems was defined.

In response to a medium-strength stimulus which is intermediate between the strong and the weak ones, a symptom complex of reaction developed. Lubov Garkavi, the author of the discovery, has named it activation reaction (4). A multiparametric research of the trigger mechanisms of the brain, including cortex, hypothalamus, pituitary, and monitoring of all functional body systems with defining the energetic and plastic resources, clearly subdivided the norm zone into a calm and increased activation. The difference from the physiological training reaction (T) was the speed and a high level of activation of the body’s defense systems. With the development of calm activation (CA), the most harmonious state is observed, while the physiological capabilities of the body reach the peak of the systems’ functioning efficiency with an increased activation (IA). It is these archetypes of reactions (T, CA, IA, S) that constitute the initial level, i.e. the ABC of response. Every person is endowed with such “software” to maintain the self-organization processes.

The second most important discovery was that the simple primary sequence of reactions of the same level is not so simple and is the basis of a more complicated multi-level system, namely, a periodical repetition of the eponymous reactions tetrad within a large range of (the strength of) exposure. This meant that despite the whole largest maximum scale of the absolute exposure value the body perceives, it does not invent new forms of response every time, but, like the genetic code with the four nitrogenous bases, includes different levels of reactivity from low to very high ones with the same sequence of the four types of adaptational reactions. Thus, the periodicity principle is common for the living and lifeless nature. This is also shown both with the Periodic Law by D.I. Mendeleev, and with the periodicity of repetition of eponymous reactions. Such a multi-level system defines the biological expediency of choosing an appropriate response to all diversity of exposures.



Prospective data. The processes of self-organization of living systems revealed the living dialectics not only for getting acquainted with the structure of adaptive response, but also for understanding the control levers of non-specific resistance (5). The strategies and principles of activation therapy have been developed. They can serve as a fundamental basis of accompanying treatment of any pathology and extreme states. The factors inducing anti-stress reactions, eval

Keywords: Adaptation, stress, anti-stress reactions, non-specific resistance, activation therapy, oncology.

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Endogenous Intoxication in Conjunction with Hemostatic Disorders in Acute Peritonitis

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Relevance: At the moment, special attention is paid to the study of the pathogenetic foundations of acute peritonitis. This is due not only to the relatively high frequency of the disease, but also to significant mortality [1]. Studies emphasize that the main link in the pathogenesis of acute peritonitis is endogenous intoxication, which causes a cytokine reaction, activation of lipoperoxidation, systematization of inflammation, respectively, multi-organ dysfunction, especially liver. Hepatic depression, in turn, leads to the activation of blood clotting, the development of microthrombosis in the capillary bed and microcirculatory disorders, aggravating the course of the disease [2].

Purpose: To determine the pathogenetic relationship of the toxic reaction with the functional state of the hemostasis system in patients with acute peritonitis.

Material and methods: The study analyzed 30 patients with acute peritonitis of different genesis. They were divided into 2 groups depending on the severity: the first (control, n=15) – with a mild degree, age – 30.2±3.1 years, men were 10 (66.6%), women – 5 (33.3%); the second (study, n=15) – with a severe degree, age – 46.3±6.8 years, men – 8 (53.3%), women – 7 (46.6%). To compare the studied parameters with the reference value, healthy people (n=10, age 18-50 years) were examined. Participation criteria: personal consent, age – 20-65 years, duration of illness less than 48 hours, mild concomitant diseases, treatment – surgical. Exclusion criteria – own refusal from the study; the duration of the disease is more than 48 hours; the presence of severe concomitant pathologies, including tumors.

Surgical treatment – elimination of the cause of peritonitis, sanitation and drainage of the abdominal cavity. Before the operation, patients underwent preparation, including antibacterial, infusion, antispasmodic, etc. components.

Research methods: In addition to the generally accepted standard (clinical, laboratory, instrumental methods), the degree of intoxication (effective (EAC) and total (TAC) albumin concentration) and the state of the blood hemostasis system were determined using the TEG® 5000 Thrombelastograph® (USA) - reaction time (R), coagulation index (CI)

Study periods – before surgery (1st day), 3rd and 8th postoperative days.

The statistical analysis of the obtained results was carried out according to the Statistica 7.0 program and the inclusion of Fischer, Student, Hardy-Weinberg criterion.

Results and discussion: When assessing the degree of endotoxemia in acute peritonitis, it was found that in the control group, the concentrations of EAC and TAC were reduced by 21.7 and 25.3% on the day of hospitalization ($p < 0.05$). On the 3rd day, the values of the indicators increased,



but remained below the reference level by 16.5 and 20.9% ($p < 0.05$). By the last (8th postoperative day), these parameters corresponded to the norm.

In the main group (with severe acute peritonitis), the indicators of endotoxemia (EAC and TAC) were lowered relative to the norm at all stages of follow-up by 35.4-22.7 and 40.1-29.6% ($p < 0.05$). When studying the functional status of the hemostasis system, it was demonstrated that the development of hypercoagulation and hypofibrinolysis was noted in patients with acute peritonitis. On the day of hospitalization of patients of the first group, the coagulation time (R) was reduced relative to the baseline level by 28.2% ($p < 0.05$). In the postoperative period (day 3), an increase in the parameter R was recorded, but it was shorter than the norm by 19.5% ($p < 0.05$). On the final (8th) day, this parameter was very close to the reference level. At the same time, fibrinolytic activity was inhibited at the first and second stages of observation. The CI time exceeded the reference time by 32.2 and 17.4% ($p < 0.05$), respectively. At the last stage, the restoration of fibrinolytic ability was noted.

In the second group (severe acute peritonitis), the coagulation reaction time was 40.6% lower than normal ($p < 0.05$). On the 3rd day after surgery, the value of R decreased, but remained below the normal level by 31.4% ($p < 0.05$). On the 8th postoperative day, a significant increase in the R value was found, but it remained above the reference value by 17.5% ($p < 0.05$).

The fibrinolysis index (CI) exceeded the normal value: before surgery by 58.9% ($p < 0.05$), after it on the 3rd - by 37.8% ($p < 0.05$) and on the 8th day by 22.2% ($p < 0.05$).

Consequently, the development of endogenous intoxication in patients with acute peritonitis is associated with a violation of the functional status of the hemostasis system, and is associated with the severity of the disease. This is confirmed by a significant difference in the values of the studied indicators. In the main group, compared with the control, the differences were as follows: EAC – was lower by 15.7-13.6% ($p < 0.05$), TAC – by 18.9-14.2% ($p < 0.05$), R – shorter by 14.4-12.7% ($p < 0.05$), CI – longer by 16.1-13.2 % ($p < 0.05$).

Conclusion: Pronounced endogenous intoxication, which develops in the initial stages of acute peritonitis, causes significant disorders in the hemostasis system in the form of hypercoagulation and hypofibrinolysis. The magnitude of hemostatic disorders was associated with the severity of the disease: with a mild degree, the changes were reversible, and with severe – persistent.

Keywords: Endogenous intoxication, hemostasis disorders, acute peritonitis

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Lung Lesions in Acute Surgical Pathology of the Abdomen

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Relevance: Despite modern successes in diagnosis and treatment, acute abdominal diseases still remain in the focus of surgery [1]. The development of severe diseases leads to high mortality, often caused by multi-organ lesions. Their number could be 59.8–95.1%. It is early insufficiency, characterized by dysfunction of the lungs, heart, liver, kidneys, cardiovascular, hepatic, etc. It is the cause of disease progression and high mortality [2].

Purpose: To determine the functional state of the lungs in acute surgical pathology of the abdomen.

Material and methods: Research material – 40 patients with emergency surgical pathology, including acute pancreatitis, acute cholecystitis, acute intestinal obstruction, acute appendicitis. According to the APACHE II scale, patients were divided into groups: 1st (comparison, n=20) group - with mild severity, women – 10 (50.0%), men – 10 (50.0%), age – 50.4±2.8 years; 2nd (main, n=18) group – with severe degree, women – 11 (55.0%), men – 9 (45.0%), age – 52.2 ± 4.1 years. The study examined 12 relatively healthy individuals.

Inclusion criteria – personal consent, duration of the disease less than 72 hours, age - 25-65 years, mild comorbidities. Exclusion criteria – own refusal, pathology period of more than 4 days, age younger than 25 years and older than 65 years, severe concomitant diseases.

Methods – determination of lung function (by creatinine, bilirubin, medium-weight molecules (MWM), aspartate aminotransferase (AsAt), toxicity index (IT)) in mixed venous blood (MVB) (inflow to the lungs) and arterial blood (AB) (outflow from the lungs) (based on organ blood flow per minute)

The observation period is the day of admission.

The research data were processed using Statistica 12.0 and Microsoft Excel 2013 programs using the Fischer, Student, and Kraskel–Wallis criteria.

Results and discussion: In the comparison group (with a mild degree), upon admission to the clinic, there was an increase in the plasma level of hydrophilic toxic products (creatinine) in the blood flowing from the lungs by 30.58% (p<0.05), and in the total venous blood by 36.9% (p<0.05). In patients of this group, an increase in bilirubin content, MWM transamine activity, plasma toxicity index in MVB was also recorded – by 15.7, 32.4, 19.5 and 31.3% (p<0.05), respectively, and in AB by 12.5, 19.1, 14.1 and 21.3% (p<0.05), respectively

In severe cases, the severity of respiratory dysfunction of the lungs was subject to significant changes, which indicates that lung damage is associated with the severity of acute surgical pathology.



In the main group, the creatinine content exceeded the normal level by 45.1% ($p < 0.05$) in the total venous blood. The value of amphiphilic (AsAt, MWM, bilirubin,) and hydrophobic (IT) metabolites in MVB exceeded the normal value by 20,5, 25,7, 22,3, 31,7, % ($p < 0.05$), respectively. Analysis of these parameters in the flowing (arterial) blood plasma from the lungs showed greater changes: creatinine content exceeded by 56.7% ($p < 0.05$), transaminase activity was increased by 26.5% ($p < 0.05$), bilirubin level increased by 28.7% ($p < 0.05$), MWM - by 34.1% ($p < 0.05$), IT - by 41.7% ($p < 0.05$)

So, the change in the detoxification activity of the lungs in acute diseases of emergency surgery was recorded to the greatest extent in severe cases. This was evidenced by a comparative analysis, the result of which showed the plasma level of toxic metabolites (creatinine, AsAt, bilirubin, IT, MWM) in patients of the second group exceeded the first by 14.2, 12.7, 15.1, 13.5 and 14.1% ($p < 0.05$) – in MVB and 16.9, 12.3, 17.7, 16.5 and 14.2% ($p < 0.05$), respectively, in the AB

Conclusion: The early period of acute surgical pathology is characterized by endotoxemia, leading to depression of the detoxification function of the lungs. These changes are associated with the degree of severity: in severe cases, the deviations were the greatest and persistent.

Keywords: Lung lesions, acute surgical pathology of the abdomen

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Characteristics of Adaptation Capabilities Students with Different Level of Fitness-Health

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The concept of "fitness-health" was formed in modern conditions under the influence of the mass enthusiasm of the population for fitness, and is determined on the basis of morphofunctional and bioimpedance indicators, as well as physical qualities [1].

Before other physiological characteristics, indicators of the cardiorespiratory system react to the body's adaptation to changes and physical loads [2,3]. The most informative of them is the heart rate, because. allows early detection of deviations in regulatory systems during biomedical control [2,4].

To obtain objective results of heart rate variability, investigators are encouraged to perform functional tests, such as an active orthostatic test (AOT). Despite the ease of implementation, AOT is highly informative and makes it possible to study the functional reserves of autonomic regulation by identifying the activity of the sympathetic and parasympathetic divisions of the autonomic nervous system and the central mechanisms that determine the impact not only on the cardiovascular system, but also on the body as a whole [5].

With the admission of young people to sports training fitness instructors and doctors most often do not take into account the initial functional state of regulatory systems and their adaptive capabilities, which is one of the reasons for the rapid onset of dysregulation and overtraining of the body already at the initial stages of training sessions [5,6].

The study of the dynamics of functional states that occur during training sessions is relevant, first of all, to determine the level of fitness and performance, to increase the effectiveness of rehabilitation measures involved in fitness and sports [7].

The purpose of the study is to study the adaptive capabilities of students with different levels of fitness-health.

Materials and methods: The study was conducted during preventive examinations at the Health Center of 637 students (258 boys and 379 girls) aged 18-25, including the measurement of indicators: body weight, dynamometry of the right hand, lung capacity, Stange test, heart rate, systolic and diastolic blood pressure, active cell mass, body fat mass, total water, basal metabolism. In the process of studying at the university, an assessment of the physical qualities of students was carried out. Then, according to the obtained indicators, the strength index, endurance coefficient, Skibinskaya index, component composition index, assessment of physical qualities and the level of fitness-health were calculated according to the recommendations set forth in the Patent of the Russian Federation "Method for assessing the level of fitness-health"

The degree of adaptation was determined by the method of R.M. Baevsky [8].



When conducting an AOT, we analyzed the indicators of the stress index (SI) and the ratio of the low-frequency component over the high-frequency component (LF/HF) [9].

In the course of the study, a database was formed, statistical processing was carried out using the office suite programs "EXCEL v8.00", "STATGRAPHICS Plus Version 5" and "Version 4.03 Primer of Biostatistics". In the course of the study, methods of variation statistics were used (calculation of the arithmetic mean (M) and its error), methods for assessing the reliability of the results (χ^2 test (chi-square)). Differences were considered statistically significant at $p < 0.05$.

Research results: Based on the results of examinations at the Center for Health and physical exercises from the TRP complex, the level of fitness-health of students was calculated: 6.8% have a high level of fitness-health; a good level of fitness-health - 18.0%; average level of fitness-health - 51.0%; low level of fitness-health - 24.4% ($\chi^2=20.41$; $p < 0.001$)

In the course of the study, it was determined that the majority of students with a high and good level of fitness-health have satisfactory adaptation (84.4%), as well as tension in adaptation mechanisms (88.1%). Failure of adaptation among these groups of students was not revealed. Students with low fitness-health are dominated by indicators of unsatisfactory adaptation (66.3%), and among them more than in other groups, boys and girls with a breakdown in adaptation mechanisms (27.9% and 14.8% respectively).

The values of SI in students with high fitness-health are 2 times less than in students with low fitness-health: 35.9 and 87.4, respectively, and after the AOT, the values of SI in students increase to 56.6 (with high fitness-health) and up to 114, 3 with low fitness-health.

When studying the spectral analysis of students with low and medium levels of fitness-health, a significant predominance of the low-frequency component over the high-frequency component (LF/HF) was noted, the ratio of which decreases with an increase in the level of fitness-health: a high level of fitness-health is 0.66 ± 0.11 ; good level of fitness-health - 0.82 ± 0.28 ; average level of fitness-health - 1.19 ± 0.37 ; low level of fitness-health - 2.44 ± 0.73 .

A decrease in LF/HF indicates the predominance of parasympathetic influences.

Conclusion: The results of the study showed a high level of adaptive capacity in students with good and high fitness-health, which is confirmed not only by determining the degree of adaptation according to the method of R.M.Baevsky, but also by the indicators of variational pulsometry and spectral analysis.

In students with low fitness-health, an increase in the centralization of heart rate control is noted, due to an increase in the activity of the sympathetic department, which occurs against the background of a decrease in parasympathetic influences on the sinus node.

In students with high fitness-health, the optimal functional state was determined, which is characterized by a balance in the activity of the parasympathetic and sympathetic departments. The reaction of the body to AOT in them occurs with a moderate tension in the mechanisms of the central regulation of the heart rhythm.

Thanks to systematic sports training, adaptive shifts of a general nature are formed in the body, due to physiological, structural and biochemical changes [10]. The high level of fitness-health, which is the result of physical education and sports training, is reflected in the functional state of regulation, which is trained and improved under the influence of systematic physical activity.

Keywords: fitness-health, adaptive capabilities, stress index



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Experimental Modeling in Solving Topical Oncology Issues

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Despite the advances in modern medicine, cancer and especially its later stages are still difficult to cure, and it claims millions of lives every year. It is often combined with other diseases, such as pain, endocrinopathies, and immunodeficiencies. However, it is not clear how malignancy and concomitant pathologies are combined in one organism.

Currently, pain is not treated as a symptom or symptom complex, but as a disease requiring specialized treatment [1]. Pain is widespread in cancer patients; it can manifest non-cancer chronic diseases, 65–90% of patients experience pain with tumor progression, in 30–50% of cases it accompanies anticancer treatment, and 33% of patients suffer from pain after the end of treatment [2]. Pain mechanisms in cancer can combine neuropathic and nociceptive components [2].

In order to study pathogenetic characteristics of malignant tumor development in presence of chronic neurogenic pain (CNP), we modeled pain by ligation of the sciatic nerves and transplanted the tumor material subcutaneously after 2-3 weeks in mice and after 1.5 months in rats. CNP stimulated the growth and metastasis of B16 melanoma in C57Bl/6 mice, and this effect was more pronounced in females. The growth of tumors in presence of CNP in females became bifocal, while in males it remained single-focal; metastasis occurred three weeks earlier than in females without pain and one week earlier than in males with pain, including metastasis to atypical sites (heart, uterus), while males showed only an increased number of metastases to the lungs [3, 4]. C57BL/6-Plau mice have a target mutation that provides the synthesis of a defective urokinase-type plasminogen activator protein that is unable to bind to its receptor. Reproduction of CNP preceding the inoculation of B16 melanoma in such mice annihilated the genetically determined inhibition of tumor growth [5]. Under the influence of CNP, Guerin's carcinoma lost its sex specificity and in 100% of cases was reproduced by subcutaneous inoculation in male outbred rats [6], and M1 sarcoma cells, when injected into the subclavian vein of male rats, gave rise to tumor foci in the lung [7] which was impossible without CNP.

The incidence of diabetes mellitus increases along with increasing cancer incidence. Up to 20% of people with cancer have diabetes [8]. We established that the growth of Guerin's carcinoma in presence of diabetes in white outbred female rats was progressively metastatic and affected many internal organs [9], while diabetes in males resulted only in larger volumes of the primary tumors. Diabetes was initiated by intraperitoneal aloxan in a single dose of 150 mg/kg, tumor material was transplanted subcutaneously with the development of persistent hyperglycemia [9].



The role of thyroid dysfunction in cancer has not yet been determined. The effect of hypothyroidism, a clinical syndrome associated with deficiency of thyroid hormones, on tumor growth was the most debatable. An experimental model of hypothyroidism was created by oral administration of Merkazolil during 30 days in a daily dose of 2.5 mg/100 g of weight. Hypothyroidism was diagnosed by the serum levels of thyroid hormone (increase) and thyroxine (decrease), and then Guerin's carcinomas were transplanted subcutaneously [10]. Females showed inhibition of tumor growth during the whole observation period, while in males such inhibition was registered only at an early stage, during the first two weeks after the transplantation, and then the effect disappeared. Perhaps females were more sensitive to hypothyroidism due to the interconnection of metabolism of thyroid hormones and estrogens.

Balb/c Nude mice with primary immunodeficiency due to thymus aplasia are the optimal platform for studying pathogenesis of multiple tumors. Several variants of multiple subcutaneous tumors were created, and the behavior of the tumors differed from that in their independent growth. Thus, as a result of the sequential transplantation in females, the malignant potential of B16 melanoma decreased and the activity of Guerin's carcinoma increased as its growth and metastasis were stimulated; the carcinoma almost completely suppressed the growth of melanoma visualized as a small dark spot within 5 mm in diameter located on the carcinoma surface under the skin at the site of inoculation of melanoma cells [11]. In males with transplanted sarcoma 45 and B16 melanoma, the malignant potential of both tumors increased. Interestingly, we noted metastasis of melanoma under the sarcoma capsule [12]. Subcutaneous transplantation of B16 melanoma and Lewis lung carcinoma in females caused the growth of B16 melanoma and the suppression of the carcinoma growth. In males, the growth of B16 melanoma contributed to the growth of Lewis carcinoma which could not be reproduced independently [13]. Melanoma became the donor of estrogens, in particular, estrone for Lewis lung carcinoma, which allowed for its development in males.

Secondary immunodeficiency associated with tumor growth or antitumor treatment is more frequent in cancer practice. We created a similar situation in an experiment with white outbred male rats with sarcoma 45 cells administered into their spleen which was previously removed under the skin [14]. The main effect of the model included sequential metastasis from the primary tumor to the liver and from the liver to the lung, to a greater extent due to the metabolism of the perifocal area of liver metastases. Studying the influence of secondary immunodeficiency on cancer further, we administered B16 melanoma cells into the spleen of a white outbred rat and obtained a model of combined hematogenous lymphogenic metastasis totally affecting somatic organs and organs of the lymphoid system [15].

Thus, experimental modeling is still a demanded tool in practical oncology allowing understanding of many unknown links of malignant pathogenesis.

Keywords: Cancer, chronic pain, endocrinopathies, immunodeficiency, experimental modeling, B16 melanoma, sarcoma, carcinoma, mice, rats.

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Neurotransmitters of Cerebral Cortex in Transplanted B16/F10 Melanoma Growing in Presence of Chronic Neurogenic Pain

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Research on the pathogenesis of chronic neurogenic pain (CNP) has developed exponentially in the last decade. Numerous findings indicate that chronic pain of various geneses is characterized by specific neuroplastic changes in the peripheral and central nervous system manifesting themselves as a generalized hypersensitivity of the somatosensory system. In addition to hypersensitivity of ascending nociceptive transmission, there is also evidence of abnormalities in endogenous descending systems of nociceptive modulation [1]. One of the main concepts that have emerged from pain research is that CNP is both a disease of primary sensory neurons and the spinal cord, and also of the brain. The abnormalities include ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity, and formation of new synaptic patterns and neuroimmune interactions.

The purpose of this study was to determine levels of biogenic amines and serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in the cerebral cortex of mice in the dynamics of growth of experimental B16/F10 melanoma reproduced in presence of CNP.

The experiment included male and female C57BL/6 mice (n=132) aged 8 weeks with an initial weight 21-22 g. The animals were divided into groups: two control groups with intact mice (n=7 males and females each) and mice with a CNP model (n=7 males and females each), comparison group with mice with a standard subcutaneous transplantation of B16/F10 melanoma 0.5 ml diluted 1:10 in saline (n=22 males and females each), and main group with mice with B16/F10 melanoma transplanted 2 weeks after the CNP model creation (n=30 males and females each). CNP was reproduced by bilateral ligation of the sciatic nerves [2]. Mice of the main group and the comparison group were decapitated after 1 week of tumor growth with subsequent isolation of the cerebral cortex. Mice in the control groups were decapitated 3 weeks after ligation of the sciatic nerves. The levels of biogenic amines: serotonin, histamine, adrenaline, noradrenaline, and 5-HIAA were determined by ELISA in cerebral cortex tissue homogenates (Cusabio, China).

As well as the growth of B16/F10 melanoma, CNP had a stressful effect on the body. The response of the neurotransmitter brain systems to these influences had sex differences. In females, CNP maximally changed the levels of biogenic amines in the cerebral cortex: levels of histamine, adrenaline, noradrenaline and serotonin decreased with the accumulation of 5-HIAA; the changes in males were minimal: only adrenaline decrease was detected. The effect of B16/F10 melanoma



development in presence of CNP in male and female mice of the main group on the neurotransmitter status of the brain also had its sex differences and common features. Levels of adrenaline and noradrenaline increased and the level of 5- HIAA decreased, while histamine was unchanged, in male and female animals of the main group at the stage of tumor onset 1 week after melanoma transplantation, compared with the control. The sex differences were the following: in females, the levels of serotonin and dopamine in the brain increased, while in males only serotonin decreased and the level of dopamine did not change. The initially low level of serotonin in females of the control group probably led to a breakdown in the adaptive capabilities of their body and disrupted nervous, antinociceptive, vegetative and metabolic mechanisms of regulation. This assumption was confirmed by a sharp deterioration in the tumor course expressed in lower survival, early metastasis, and a shorter latent period of melanoma in females. The same applied to histamine, since its decrease in the cerebral cortex of females under the influence of chronic neuropathic pain reflected the inhibitory antinociceptive influence of this brain structure which reduced the mediator activity of histamine. The monoamine pathway, especially noradrenergic and serotonergic transmission, was established as the main component of the endogenous antinociceptive system [3]. Monoamine neurotransmitters can be maintained either by inhibiting their uptake or by inhibiting their metabolism through the monoamine oxidase (MAO) mechanism. MAO has two types, A and B, according to their sensitivity to specificity substrates and to acetyline inhibitors. The results of this study confirm this position: we found that decreased serotonin in the cerebral cortex of females of the main group was accompanied by an increased level of its metabolite 5-HIAA, which was the result of MAO-A activity. This can be extrapolated to other monoamines, noradrenaline and adrenaline, which are also MAO-A substrates. On the contrary, such a pattern was not observed in the males of the main group, since decreased serotonin in them was accompanied by decreased 5-HIAA. Previous studies showed that neurotoxic or induced by sciatic nerve injury hyperalgesia can be reduced by MAO-A inhibitors [4]. Xu et al. (2016) suggested that mice with sciatic nerve injury had an increase in MAO-A activity, while ferulic acid changed MAO-A activity and restored monoamine levels [5]. This further indicates that MAO-A in females could be closely associated with downstream neurotransmitter dysfunction underlying neuropathic pain.

The results of this experiment demonstrated the modifying effect of comorbid conditions on cancer course, with possible acceleration of the natural history of neoplastic development.

Keywords: Cancer, chronic pain, B16 melanoma, biogenic amines, brain, mice

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Neurotrophin Response of the Brain to Malignant Tumor Growth in Presence of Hypothyroidism in The Experiment

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The prevalence of thyroid dysfunction and cancer, their systemic nature actualize the study of the pathophysiological mechanisms of the possible relationship of these pathologies. Information has been accumulated on the relationship of innervation and regulatory molecules between a malignant tumor and the nervous system of a tumor-bearing organism, which indicates a significant role of the nervous system in regulating cancer development and progression and may be caused by brain neuroplasticity [1]. We have shown a change in the pathophysiological parameters of the tumor growth, which has sex differences, and the functioning of the hypothalamic-pituitary-thyroid axis (HPT axis) in rats with the growth of Guerin's carcinoma in presence of induced hypothyroidism [2,3]. It is interesting to evaluate the content of members of one of the families of neurotrophins in the cortex (gray matter) and in the subcortical (white) matter of the cerebral hemispheres of rats of both sexes during extracerebral growth of a malignant tumor in presence of induced hypothyroidism, which was the purpose of this study.

An experiment was performed in white non-linear female (n=47) and male (n=47) rats: intact group (n=20); control group 1 with induced hypothyroidism (n=20); control group 2 with subcutaneous growth of Guerin's carcinoma (n=20); main group with a combination of the pathologies (n=20); group with subcutaneous tumor growth to assess life expectancy (n=14). Hypothyroidism was induced by per os administration of thiamazole (mercazolil, Akrikhin, Russia), daily dose of 2.5 mg/100 g of body weight, course of 30 days; total thyroxine and thyroid stimulating hormone were determined in blood serum by RIA (Immunotech, Czech Republic). After persistent hypothyroidism, Guerin's carcinoma was transplanted under the skin using standard methods. After decapitation on day 18 after the transplantation, levels of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF- β), neurotrophin 3 (NT3) were determined by ELISA in 10% homogenates of the gray and white matter of the brain (R&D System, RayBiotech, USA).

In the group of females with hypothyroidism, the most pronounced changes were observed in the gray matter: the BDNF and NT3 levels were lower by 2.6 and 3.0 times, respectively, and NGF- β was higher by 2.2 times than in the intact group; in males, changes were observed in both gray and white matter: there was also a lower level of BDNF by an average of 2.1 times, the NGF- β level in the gray matter was lower, and in the white matter it was higher by an average of 1.4 times ($p < 0.001$) than in the intact group. In the group with tumor alone, rats of both sexes had a lower level of BDNF in the gray matter by an average of 1.5 times ($p < 0.001$); the NGF- β level increased in



females in the gray and white matter by 2.2 and 3.1 times, respectively, in males only in the white matter by 2.0 times; the NT3 level was higher than in the intact group, in males only in the gray matter by 1.7 times ($p < 0.001$), and in females by 2.4 times only in the white matter. In the group with comorbidity, statistically significant changes were noted in females only for NGF- β with an increase in its level in the gray and white matter by an average of 1.7 times ($p < 0.001$); in males, only the BDNF level in the gray matter was lower by 3.2 times, while in the white matter the BDNF level was 1.6 times lower ($p < 0.001$), the NGF- β and NT3 levels were higher by 1.9 and 1.5 times respectively ($p < 0.001$).

Thus, the most pronounced changes in the BDNF level were noted in female rats in the gray matter in groups with hypothyroidism and with a tumor alone, and in male rats in the gray and white matter in groups with hypothyroidism and with comorbidity. The NGF- β level changed more significantly in groups with tumor growth: in female rats both in gray and white matter, in male rats only in white matter. Changes in the NT3 level were most significant in female rats with hypothyroidism and in the group with tumor alone, while in male rats, only in groups with tumor growth. Our results provide new information about the functioning of the neurotrophin system in the brain during the development of an extracerebral non-thyroidal tumor and confirm the interaction of a growing tumor (both alone and in combination with thyroid dysfunction) with the central nervous system (CNS) within the framework of the neuroplasticity phenomenon. The revealed decrease in the BDNF level and a significant increase in the NT-3 and NGF content in the gray and white matter of the brain of rats with a tumor alone probably indicate a change in the balance towards deterioration of synaptic plasticity in the cortex and activation of axono- and synaptogenesis processes in the subcortical areas of the brain, and the possible activation of neuronal regulation of the tumor stem cell compartment through NT-3 regulation, which in total accompanies active subcutaneous tumor growth. A less pronounced change in the NGF, BDNF and NT-3 levels with comorbidity may be associated with differences in pathophysiological parameters, both combined with hypothyroidism (growth inhibition), and an independent tumor process at the same observation period. Moreover, a change in the balance of regulatory signals in the cortex and in the subcortical (more ancient) areas of the brain may be associated with the HPT axis dysfunction during the development of an independent tumor process in the body, both at the level of the hypothalamic-pituitary tract and at the level of the pituitary-thyroid interaction [2]. Some features of changes in the content of neurotrophins in female and male rats may be associated with differences in the course of the experimental tumor process in animals of different sexes [2,3], as well as the existence of known sex differences in the functioning of the HPT axis and CNS responses to the effects of thyroid hormones, due to complex sexual differentiation of the brain [4]. On the whole, our results confirm the close interaction between the CNS and extracerebral tumors, the modifying effect of comorbid pathologies, and constitute the basis for further studies of the central mechanisms of regulation of the body functioning in presence of malignant tumor growth.

Keywords: Hypothyroidism, tumor process, comorbidity, experimental model, brain, neurotrophins, sex differences, brain-derived neurotrophic factor, nerve growth factor, neurotrophin 3



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Experimental Myocardial Infarction Occurs When a Malignant Process is Combined with Chronic Neurogenic Pain

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In the case of chronic pain sensations, functional changes occur in the life support systems of the body [4]. Two global problems of medicine are associated with oncology and cardiovascular pathology, and taking into account the prevalence of pain symptoms of various etiologies, a pathological triangle is formed, each side of which affects the overall configuration. There is a need to understand these pathological relationships in order to determine the real possibilities of breaking them and changing such common and complex pathological combinations. Undoubtedly, experimental modeling of pathological conditions [1-3] with the identification of key dysfunctional pathways supplemented by visualization of real pathological changes in the heart is a highly relevant research area.

Purpose: To study the morphological pattern of the heart in female mice with chronic neurogenic pain (CNP) and B16/F10 melanoma growth.

Materials and methods: Female C57BL/6 mice (n=48) were used in the research. Chronic neurogenic pain (CNP) was created by bilateral ligation of the sciatic nerve in animals under xylazoethyl anesthesia. 3 weeks after the healing of the surgical wound, all animals underwent subcutaneous transplantation of B16/F10 melanoma under the right shoulder blade in a volume of 0.5 ml of cell suspension in physiological saline at a dilution of 1:10 (2.7x10⁶ cells); cells were counted using ADAMII-LS analyzer (Nano Entek, Korea). Mice were decapitated at the time of B16/F10 melanoma growth: 1st, 2nd and 3rd weeks. After decapitation, the isolated heart preparations were carried out according to the stages of morphological preparation for hematoxylin and eosin staining of sections, followed by morphological control of the structure based on Leica DM LS2 microscope with Olympus optical.C-5050 Zoom video camera and Morfotest software. Photographing was conducted with magnifications x10, x40, x100.

Results: During the experiment, female mice were found to have a myocardial infarction that occurs with comorbidity (CNP+B16/F10 melanoma). Myocardial infarction started to be recorded from the first week of melanoma growth in presence of CNP, and the number of females with damaged myocardium progressively increased until the end of the malignant process development (3 weeks). At the same time, a pronounced pro-oncogenic effect of pain stimulation of a neurogenic nature was established; the effect consisted in an earlier manifestation of tumor growth, large



metastasis even in atypical target organs, and the formation of a pre-terminal state within a shorter period of time. Morphological control of animal heart preparations made it possible to give some visual representations of the cardiac muscle state in presence of systematic neurogenic pain as a background condition for the development of oncological pathology. Moreover, morphological correlates of heart disease at the level of valves and the ventricular wall were determined; the key elements of heart disease were ischemia, total longitudinal splitting of muscle fiber bundles, blood filling of large vessels, hemorrhages, deep cardiomyocyte degeneration, myolysis, macrofocal necrosis (myomalacia), accumulation of necrotic masses, fibrosis, eosinophilic infiltration. Visualization of the cardiomyocyte nuclei indirectly indicated the switching of the death program to the non-apoptotic pathway, i.e. necrosis as a result of "tumor" depletion of the cardiomyocyte energy reserves.

Conclusion: The morphological study of changes in the heart in female mice on pathological models of chronic neurogenic pain and malignant tumor growth made it possible to reproduce the catastrophe of a highly organized cellular system of the implementation of hemodynamic processes. The simulated hypertrophic manifestations of myocardial catastrophe in the experiment expand the concept of infarction and give grounds to predict and prevent the negative course of events in difficult patients with persistent pain syndromes and comorbid pathology in presence of the malignant process development.

Keywords: Chronic neurogenic pain, B16/F10 melanoma, heart, morphological myocardial alterations, female mice

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Regulatory Axes of Adaptation in Experimental Hypothyroidism in Rats with Malignant Growth



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The adaptive response of the three main regulatory axes, hypothalamic-pituitary-thyroid (HPT), gonadal (HPG) and adrenal (HPA) ones, to internal changes in the central or peripheral links and to external influences is crucial for maintaining the body homeostasis (1). Any dysfunction of the thyroid gland, both insufficient and excess production of thyroid hormones (TH), can be a factor contributing to the development of various diseases, including malignant tumors; however, the complexity of the molecular mechanisms controlled by TH and cross-interactions with steroid hormone receptors make the data on the impact of thyroid dysfunction on cancer development risks very contradictory (2,3).

The purpose: To study the effect of induced hypothyroidism on the growth of Guerin's carcinoma and to identify the functional features of the main regulatory axes in female rats.

This experiment included 80 white outbred female rats. Hypothyroidism was induced by per os administration of thiamazole at a daily dose of 2.5 mg/100 g of body weight during 30 days, and then confirmed by RIA (Immunotech, Czech Republic) detection of blood serum levels of thyroxine (T4) and TSH. Animals were divided into groups: a group with hypothyroidism (n=20), main group (n=20) with rats with hypothyroidism and subcutaneously transplanted Guerin's carcinoma, control group (n=20) with Guerin's carcinoma only and intact group (the norm, n=20). Animals were decapitated 18 days after the transplantation of Guerin's carcinoma, and ELISA (Cussabio, China) was used to determine thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and gonadotropin-releasing hormone (GnRH) in the homogenates of the hypothalamus; TSH, LH, FSH and ACTH in the pituitary; free and total thyroxine and triiodothyronine in the thyroid; testosterone (T), estradiol (E2), estrone (E1), progesterone (P4) in the gonads; cortisol in the adrenal glands; and TH in tumor samples. Statistical analysis assessed the conformity of the distribution in the samples to the normal distribution (Shapiro-Wilk test), the statistical significance of differences was identified by the Mann-Whitney test; the Statistica 10 program was used.

4 days after the transplantation, subcutaneous tumors appeared only in 80% of females in the main group, compared to 100% in the control group, tumor volumes increased 1.5 times slower at all stages ($p < 0.05$), and the survival was 1.6 times better ($p < 0.05$). Differences in the dynamics of tumor growth under the influence of hypothyroidism could be associated with dysfunctions of the central and peripheral links of the main adaptive axes.

First, we studied the effect of induced hypothyroidism on regulatory axes in comparison with that in intact animals. Female rats with hypothyroidism showed a decrease in TRH by 2.9 times, CRH



by 1.3 times and GnRH by 1.8 times ($p < 0.05$) in the hypothalamus; however, only FSH decreased by 3.9 times and ACTH by 1.4 times ($p < 0.05$) in the pituitary, while other tropic hormones had no significant differences. Levels of total TH forms decreased in the thyroid under the influence of hypothyroidism: T4 by 24 times, T3 by 2.5 times, but free fractions increased by 1.6-2.6 times, E2 and P4 increased in the gonads by 2.1 and 2.6 times, but T decreased by 1.7 times ($p < 0.05$), and cortisol decreased by 1.8 times in the adrenal glands ($p < 0.05$).

Rats with an independent tumor growth (control group) showed the following changes compared with the values in intact animals: TRH in the hypothalamus decreased by 2.1 times, GnRH increased by 1.4 times ($p < 0.05$), and no changes in the CRH. Only a decrease in FSH by 2.1 times was noted in the pituitary, while other tropic hormones did not change. Total forms of TH decreased by 2.6-3.1 times in the thyroid, but free fractions increased by 1.6-2.6 times; an increase in cortisol by 1.3 times and P4 by 2.7 times were registered in the gonads and adrenal glands, together with a decrease of E2 by 2.6 times and T by 1.3 times ($p < 0.05$).

Animals of the main group, compared to controls, had lower levels of CRH in the hypothalamus by 1.4 times, and TSH by 1.5 times and FSH by 3.6 times ($p < 0.05$) in the pituitary; the levels of TRH, GnRH, LH and ACTH had no significant differences. The levels of total and free TH in the thyroid of females of the main group were lower than in the control group by 2-4.9 times; in the gonads, E2 was twice higher, T 1.8 times higher and P4 1.7 times higher ($p < 0.05$); cortisol in the adrenal glands returned to normal. Levels of T4, FT4 and FT3 in tumor samples of females of the main group were 1.6-2.8 times lower than in controls, E2 was 1.4 times lower, but T and P4 were higher on the average by 1.7 times ($p < 0.05$).

Hypothyroidism alone influenced the HPT axis, but also HPA and HPG, which again confirmed their close relationship in the body. Hypothyroidism and a malignant tumor alone had similar effects on some links of the regulatory axes, decreasing TRH, FSH and total forms of TH in the thyroid and increasing T and P4 in the gonads, while the opposite effect was observed in other ones: GnRH and CRH in the hypothalamus, ACTH in the pituitary, free fractions of TH in the thyroid, E2 in the gonads, and cortisol in the adrenal glands. The two pathological processes were combined in the main group of animals, modifying the responses of all units of the adaptive systems and affecting local levels of the studied hormones in the tumor.

We suggest that a decrease in CRH in the hypothalamus, ACTH in the pituitary, and normalization of cortisol levels in the adrenal glands were among the most important factors inhibiting the growth of transplanted tumors in female rats in presence of hypothyroidism. In addition, induced hypothyroidism in animals of the main group led to a decrease in the TSH content in the pituitary, disrupted accumulation of free forms of TH in the thyroid, and a decrease in the levels of TH and estradiol directly in the tumor tissue. Both TH and sex steroids can directly bind to nuclear receptors and act as transcription factors mediating intracellular effects (4); in this case, their decreased levels in the tumor could inhibit its growth.

Thus, induced hypothyroidism slowed down the growth of subcutaneously transplanted Guerin's carcinoma in female rats and improved the average survival by modifying the response of the central and peripheral links of the regulatory axes, as well as affecting the local levels of hormones in the tumor



Keywords: Hypothyroidism, Guerin's carcinoma, regulatory axes, hypothalamus, pituitary gland, thyroid gland

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Functional Activity of the Brain in Metastasis Modeling in The Lungs of Rats

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Metastasis from malignant tumors is the main cause of death in cancer patients and one of the important problems of clinical oncology. Distant metastases from malignant tumors to the lungs are most frequent. The lungs are the most common target and in 60-70% of cases remain the only site of distant metastases for some tumors, such as soft tissue sarcomas, kidney cancer, uterine chorionepithelioma, and some others [1]. A malignant tumor is a powerful disruptor of body homeostasis, and its development and progression is accompanied by the formation of some paraneoplastic disorders associated, among other things, with brain metabolism [2]. The main functions of the body are under the control of the cerebral cortex and three hormonal axes of regulation: thyroid, adrenal and gonadal ones, and their central link is represented by the hypothalamus and pituitary gland.

The purpose of this study was to analyze the levels of biogenic amines in the brain structures and tropic hormones in the pituitary gland in rats with experimental metastasis to the lungs.

Material and methods: The study was performed on 230 white outbred rats of both sexes weighing 200-250 g kept in standard vivarium conditions. Lung metastasis was modeled by injecting sarcoma 45 (S-45) cells into the subclavian vein in a volume of 0.5 ml containing 2 million tumor cells and sterile saline.

From the first week of introduction of tumor cells into the subclavian vein, half of the rats were subjected four times a week to combined exposure to an extremely low frequency magnetic field (ELFMF) in the projection of the pituitary gland and to electroneuroregulatory effects (SCENAR) on the skin in the projection of the lungs. After one and five weeks of tumor growth, the rats were decapitated. The ELISA method was used to study the levels of biogenic amines in the brain: dopamine, noradrenaline, and serotonin, as well as adrenocorticotrophic hormone (ACTH), prolactin, luteinizing (LH) and follicle-stimulating (FSH) hormones in the pituitary (Cusabio, China).

Lung tumors in males were formed within 3-4 weeks after sarcoma 45 cell injection into the subclavian vein, in females within 5-6 weeks. Males died from significant lung metastasis on day 38±3.5, females on day 182±7.0, and the area of metastatic lung damage was significantly smaller than in males.



The reaction of the pituitary gland to the development of lung metastases had pronounced gender differences. After one week of tumor growth, males showed a doubled increase in prolactin levels and multidirectional changes in the levels of LH and FSH resulting in a decrease in their ratio by 4.5 times; in females showed a decrease in prolactin levels by 1.6 times ($p < 0.05$) without changes in gonadotropins. The level of ACTH increased by 1.6 times ($p < 0.05$) in males and 1.2 times ($p < 0.05$) in females. Five weeks after tumor transplantation, pituitary prolactin levels in males decreased by 3.2 times compared to the previous study period, and the FSH/LH ratio decreased by 14.0 times; in females, prolactin increased up to initial values, the levels of LH and FSH increased by 1.7 times ($p < 0.05$) and 2.0 times, respectively, without changing their ratio.

Sex differences in the levels of biogenic amines in the pituitary gland in rats with lung metastases were expressed already a week after transplantation: in males, the level of dopamine decreased by 7.7 times compared with intact males, the levels of noradrenaline and serotonin were normal. Females were characterized by a sharp increase in the concentrations of all pituitary monoamines: dopamine by 4.1 times, noradrenaline by 3.4 times, serotonin by 2.4 times. The fifth week of the lung metastases development was characterized by a sharp reduction in all biogenic amines in the pituitary gland, regardless of the sex of the rats.

Since the bioaminergic regulation of the pituitary gland is closely related to the aminergic activity of the entire brain, it was of interest to study the levels of biogenic amines in the cortex and brain stem structures. The level of dopamine decreased by 6.4 times, compared with the norm, in the cerebral cortex of males already a week after the onset of lung metastasis, while in females it decreased only by 1.8 times ($p < 0.05$). Only in males, after one week, the level of dopamine decreased by 1.5 times ($p < 0.05$) in the brainstem, while a similar tendency in females was noted only after five weeks of metastasis: the level of DA in the brainstem for the first time decreased by 2.0 times compared to normal values. One week after the metastatic growth in the brainstem, the opposite changes in the level of NA were noted: a decrease by 1.6 times ($p < 0.05$) in males and an increase by 1.3 times ($p < 0.05$) in females.

After five weeks of metastasis, the dopamine dynamics in the cerebral cortex depended on the sex of the animals: the level of dopamine in males increased to normal values, in females it decreased by 2.0 times. Males also showed an increase in the content of noradrenaline in the cortex by 2.9 times and in the brainstem by 1.8 times ($p < 0.05$) compared with the norm, while noradrenaline in the cortex of females during the entire experiment did not change. The dynamics of serotonin in the brainstem was of interest, since it coincided with the direction of changes in dopamine in the cerebral cortex: an increase by 1.8 times ($p < 0.05$) in males and a decrease by 1.9 times ($p < 0.05$) in females.

Under the influence of experimental exposure, the latent period of tumor node onset in the lungs and survival increased by 2-3 weeks in 33% of rats, which was accompanied by the restoration of the aminergic mechanisms of the pituitary gland with a predominance of stress-limiting components over stress-realizing ones. The results demonstrated an important role of the central structures of the neuroendocrine system, ensuring the adaptation of the organism, in the processes of metastasis and their gender characteristics which determine the different stress resistance of males and females to the formation of sarcoma 45 metastases in the lungs.



Keywords: Metastasis, sarcoma 45, lung, experimental model, brain, pituitary gland, tropic hormones, magnetotherapy, SCENAR

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Relationship of Hormonal, Psychological Status and Atrial Fibrillation in Patients with Chronic Heart Failure of Ischemic Genesis

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Objective: to identify the relationship between the level of sex hormones in the blood, indicators of psychological status and atrial fibrillation (AF) in patients with chronic heart failure (CHF) of ischemic origin.

Material and methods: The study of patients with stable CHF of ischemic genesis involved 30 patients with AF and 27 with sinus rhythm. In patients, the levels of estradiol (E), follicle-stimulating hormone (FSH), total testosterone (T) in blood plasma were determined, psychodiagnostics included the hospital scale of anxiety and depression, the Toronto scale of alexithymia, five-factor personality questionnaire, Cloninger's questionnaire, eight-color Luscher test.

Results: The level of E, FSH and T were within the age norms. The E level was conditionally divided into clinically significant and insignificant and did not depend on the age of the patients and the onset of their menopause. The E level was found to be associated with the presence of AF. The level of clinically significant E was associated with higher values of alexithymia and anxiety, but relatively low "consciousness". In 90% of women, clinically insignificant E was a predictor of the choice of green color for the first position, regardless of AF, CHF, FSH level, T. The levels of neuroticism and alexithymia in women were influenced by both FSH and T, and the presence of AF, and the E level turned out to be is only related to anxiety.

Conclusion: Clinically significant E was associated with AF. Women with a normal E level had a more negative emotional background, and with a lower E level, anxiety, alexithymia, neuroticism, more often greater stress resistance and high "consciousness" were less often determined. AF, as well as changes in FSH and T levels, can be an independent predictor of neuroticism and alexithymia in patients with CHF, the presence of anxiety is associated with the level of E, and depends on the presence of AF indirectly.



Keywords: Atrial fibrillation, chronic heart failure, estradiol, testosterone, psychological status.



Dopaminergic System of the Hippocampal Formation After Simulation of Surgery in the Maxillofacial Region in Rats

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Objective: to evaluate the significance of surgical trauma on the response of the hippocampal dopaminergic system in modeling surgical interventions in the nasal cavity, paranasal sinuses and alveolar process of the upper jaw in rats.

Materials and methods. Simulation of operations was carried out on male Wistar rats under general anesthesia with Zoletil 100 solution. In group 1, septoplasty was simulated (n=10). Dental implantation was performed in group 2 (n=10). In group 3 (n=10), a hole was made in the alveolar process of the upper jaw. Sinus lifting with dental implantation was performed in group 4 (n=10). In group 5 (n=10), a maxillary sinus was performed with damage to the mucous membrane of the ipsilateral maxillary sinus. Liquid chromatography with electrochemical detection was used to determine the concentration of dopamine (DA), homovanilic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), 3-methoxytyramine (3-MT) in the hippocampal formation. DOPAC/DA, HVA/DA, 3-MT/DA were also determined.

Results. The concentration of dopamine in the hippocampus, compared with the control, was significantly higher in group 5 and lower in group 4. The HVA concentration was significantly higher in group 2, group 5 ($p<0.01$) and group 1 ($p<0.05$). An intergroup comparison determined that the concentration of HVA was significantly higher in group 2, compared with the rest of the experimental groups ($p<0.001$). In groups 1, 3 and 4, this indicator was significantly lower compared to group 5 ($p<0.01$). The DOPAC level was significantly higher ($p<0.01$) compared to the control data. The concentration of 3-MT was significantly higher in groups 4 and 5 ($p<0.001$), as well as in group 1 ($p<0.05$) and in group 3 ($p<0.01$). DOPAC/DA was significantly lower in groups 2 and 4 compared with the control group ($p<0.001$), and it was also noted in the 5th group ($p<0.01$). The HVA/DA ratio, compared with the control group of animals, was significantly lower in groups 4 and 5 ($p<0.001$). The ratio is 3-MT/DA. The Mann-Whitney U-test determined that in groups 2 and 5 ($p<0.01$), as well as in group 4 ($p<0.001$), the ratio of 3-MT/DA was statistically lower than in the control group.

Conclusion. When simulating sinus lifting with simultaneous implantation and dental implantation complicated by maxillary sinusitis, there is an increase in the concentration of dopamine metabolites 3-MT, HVA and DOPAC, but at the same time a decrease in dopaminergic activity of the hippocampal formation, compared with modeling of septoplasty and simple damage to the alveolar process of the upper jaw. Surgical trauma in modeling operations in the nasal cavity, paranasal sinuses and the alveolar process of the upper jaw in rats provokes a pronounced stress response of the dopaminergic system of the hippocampus in rats, which can be interpreted as a breakdown of adaptive mechanisms and the development of maladaptation in the early postoperative period.

Keywords: dental implantation, sinus lifting, septoplasty, hippocampus, dentate gyrus, dopamine, homovanilic acid, DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA.



Effects of Molecular Hydrogen Therapy on Circadian Blood Pressure Variability, With Reference to Night

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Background: The earth revolves around its axis, causing the light and dark cycles of 24-Hours. resulting in to day and night. These rotations of the planet are associated with alteration in physiological functions which vary according to time structure of 24 hours.

Objectives: This study aims to emphasize that molecular hydrogen therapy in patients with circadian increase of blood pressure (BP) may reverse Covid-19 induced loss of dipping.

Methods and Results. Adverse effects of high blood pressure (BP) on the heart correlate better with 24-hour means of BP than with casual BP readings, to which nocturnal BP, and morning rise in BP, plays a particularly important role [5]. Under usual conditions, nighttime BP is typically lower than daytime BP. Elevated nocturnal BP (nocturnal hypertension) and disrupted circadian variation in BP emerged as independent risk factors for cardiovascular disease (CVD) and all-cause mortality. Variability in BP and HR stem from an endogenous circadian rhythm, which persists under constant conditions, and from a host of external factors, including an influence from space weather and climate. Determinants of the circadian rhythm in BP are still poorly understood. It is not well known whether they are similar or different during the day or night and how that may interact with sleep and night shift work. Night shift work is known to cause sleep disturbance, increase in night time BP along with oxidative stress and inflammation due to increase in cortisol and decrease in melatonin. While hypertensive patients with COVID-19 appear to have a poor prognosis, there is no evidence that hypertension increases the risk of new infection or adverse outcomes independent of age and other risk factors. It has been suggested, however, that hypertension and BP variability are exacerbated by acute SARS-CoV-2 immune reactions, that has been observed in a male physician, 77 years of age, presenting with COVID-19 in 2021. He had severe insomnia and increase in night-time blood pressure (BP) as shown by self-recorded data. Supplementation with hydrogen-rich water (HRW) increased oxygen saturation 10- 45 minutes after its administration in a patient with COVID-19-like symptoms. We also found that treatment with HRW in other patients with night shift work (n=9) with nocturnal rise in BP (BP >110/75 mm Hg) was beneficial in improving nocturnal increase in BP (loss of dipping) in majority of the patients. There was a significant increase in melatonin and a decrease in cortisol among these patients. After a week, BP measurements showed that BP was reduced, notably at night. Systolic(S) and diastolic(D) BP, which averaged 127.2/84.9 mmHg in April, decreased to 113.5/79.5 mmHg in June (P<0.001). It doubled in the case of SBP and DBP and increased by 85% in the case of heart rate (HR). The difference between daytime (09:00 and 13:00) and night-time (02:30 and 05:30) measurements also increased between April and June: from 1.8 to 3.4 mmHg in the case of SBP, from 0.5 to 2 mmHg in the case of DBP, and from 2.2 to 7.6 beats/min in the case of HR. The day vs. night difference, which was absent in April (P>0.10) reached statistical significance in June in the case of DBP (P=0.038) and HR (P=0.021). However,



during recovery, SBP is significantly decreased overall ($P<0.001$). The decrease in SBP is statistically significant at all six sampling times: at 02:30 ($P<0.001$), 05:30 ($P<0.001$), 09:00 ($P=0.007$), 13:00 ($P=0.012$), 16:30 ($P=0.036$) and 20:00 ($P=0.041$). The somewhat larger decrease during nighttime as compared to daytime accounts for a 107% increase in the day-night excursion in SBP.

Conclusion: The results indicate that treatment with HRW may have been helpful in the decrease in nocturnal hypertension with improvement in dipping.

Keywords. Circadian variation, night dipping, nocturnal hypertension, homeopathic treatment.

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Modeling of a Depressive-Like State

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According to WHO, 3.8% of the population experiences depression. Various socio-economic and political events contribute to the increase in morbidity. Thus, according to the monitoring data from the Institute of Psychology of the Russian Academy of Sciences, in Russia under the influence of the events of February 2022, there was an increase in anxiety-depressive symptoms in the first quarter, exceeding the indicators of the pandemic period of 2020-2021: the proportion of respondents noting symptoms of clinical depression – from 27% to 42% (among young people 18-24 years - up to 75%) [1]. Translational studies on laboratory rodents are widely used to understand the links of the pathogenesis of the disease and the possibility of correcting the depressive state. One of the first attempts to standardize depression modeling techniques and real translational techniques was made by V. Zeltzer [2], who modeled a depressive state through the development of withdrawal syndrome. In 1984, Paul Willner [3] developed criteria for the validity of the technique: similarity of symptoms; similarity of etiology and pathogenesis; to predict the improvement of the condition and relief of signs of depression under the influence of treatment. Models of depression caused by early attachment-figure separation [4], social isolation [5], olfactory bulbectomised rat [6], withdrawal syndrome [7], learned helplessness [8, 9], chronic mild stress (CMS) [10] meet all the criteria of validity.

We have tested a modification of the CMS – chronic unpredictable mild stress. The stressful effects lasted for 3 weeks. On 14th day of experiment, 36 out of 38 animals showed signs of depressive-like behavior: a decrease in sucrose consumption and a decrease in the intersection of sectors in the Hole board test. Starting from week 3, statistically significant differences in weight gain were observed in intact and experimental animals ($p < 0.05$). On the 35th day of the experiment, a statistically significant increase in the immobilization time was observed in experimental animals compared with intact rats in the forced swimming test ($p < 0.05$). In the study of serotonin levels in the hippocampus and striatum, a statistically significant decrease in the concentration of monoamines was observed in relation to intact animals ($p < 0.05$). Thus, chronic unpredictable mild stress leads to the development of a depressive-like state in rats.

Data from a pilot study on modeling by stereostatic injection of lipopolysaccharide into the hippocampus and into the third ventricle of the brain also indicate that animals develop signs of depression: reduced sucrose consumption, decreased locomotor activity, increased immobilization time in experimental animals compared to intact rats in the Forced Swim test.

Since the studied methods lead to the development of a depressive-like state in rats, they can be used to study the antidepressant activity of new drugs.

Keywords: depression, depression modeling, chronic unpredictable stress

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Neuroinflammation in the Pathogenesis of the Audiogenic Epilepsy

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Neuroinflammation plays an important role in epileptogenesis, however, most studies are performed on pharmacological models of epilepsy, while data on non-invasive, including genetic, models are practically absent. In Krushinsky-Molodkina (KM) strain rats with high predisposition to AE (intensive audiogenic seizure fit in response to the action of sound) and in the control strain "0" (not predisposed to AE), the levels of a number of pro-inflammatory cytokines were investigated using multiplex immunofluorescence magnetic assay (MILLIPLEX map Kit). Cytokine levels were determined in the dorsal striatum tissue and in the brain stem. Background levels of IL-1 β , IL-6 and TNF- α in the dorsal striatum of KM rats were significantly lower than in rats "0" (32.31, 27.84 and 38.87%, of decrease, respectively, $p < 0.05$, 0.05 and 0.01), whereas in the brain stem in the "background" state of interstrain differences in levels of these metabolites were not detected. 4 h after sound exposure, the TNF- α level in the dorsal striatum of KM rats was significantly (38.34%, $p < 0.01$) lower than in "0" rats. In KM rats, after the action of sound and the subsequent seizure fit, the levels of IL-1 β and IL-6 in the dorsal striatum were significantly higher compared to the background (35.29 and 50.21%, of increase, $p < 0.05$, 0.01, respectively). The IL-2 level in KM rats in the background state was not detected, whereas after audiogenic seizures its level was 14.01 pg/ml (significantly higher, $p < 0.01$). In the brain stem of KM rats, the levels of IL-1 β and TNF- α after audiogenic seizures were significantly lower than in the background (13.23 and 23.44% of decrease, respectively, $p < 0.05$). In rats of the "0" strain, the levels of cytokines in the dorsal striatum after the action of sound (which did not cause AE seizures) did not differ from those in the background, while the levels of IL-1 β in their brain stem were lower than in the background (40.28%, $p < 0.01$). Thus, the differences between the background levels of cytokines and those after the action of sound were different in rats that differed in their predisposition to AE, which suggests the involvement of these metabolites in the pathophysiology of epilepsy.

Keywords: audiogenic epilepsy, Krushinsky-Molodkina strain, "0" strain rats, seizures, cytokines, inflammation, IL-1 α , IL-1 β , IL-2, IL-6, TNF- α , multiplex assay.



SGLT2 inhibitors in Hypertension From a chronocardiological point of view

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Based on the positive role of SGLT2 inhibitors in treating heart failure, as these medications have become part of the protocol in treatment for heart failure, can this group play any role in the treatment of Hypertension? For this reason, we conducted a clinical study on a group of patients suffering from Hypertension associated with diabetes mellitus, SGLT 2 inhibitors was part of his treatment, compared with another group of patients, suffering from Hypertension without diabetes mellitus and without SGLT 2 inhibitors in his treatment. Those two groups were compared with a placebo group that did not take anything.

The study was conducted on 135 people: 68 women and 67 men, ranging in age 60 years and from different classes of society.

Since our country Lebanon has a moderate climate characterized by four seasons: winter - spring - summer - autumn, the study included these four seasons. In each season over a two-year period - starting from 2021 until the end of 2022 - we monitored blood pressure, weight, classical ECG, lab. analysis and Dispersion Mapping – ECG (ECG-DM) was performed for each participant. In order to evaluate the role of the seasons of the year in HTN, diabetes and its treatment. The method of DM-ECG can detect abnormalities in cardiomyocytes at early stages of pre-clinical metabolic changes. DM - ECG monitoring was performed from 20 to 90 minutes, 4 times with 3 months' intervals (spring, summer, autumn and winter).

The DM-ECG method is based on analysis of microalternations during whole cardiac cycle PQRST. Nine groups of dispersion indicators are being analyzed. They reflect microalternations of the repolarization and depolarization of myocardium. The nine groups of dispersion indicators are summarized in the form of Integral parameter (IMM) = index of myocardium microalternations = MYOCARDIUM, whose analysis and results are included in this presentation.

The study included 3 groups:

- 1- Control group. They are a healthy group, do not suffer from any disease and do not take any chronic medications. This group included 43 citizens, 13 women and 30 men. The second group included 46 Hypertensive patients (24 men/22 women). This group took chronic medications from the ACE (Ramipril, Perindopril), ARB (Losartan, Irbesartan, Candesartan), BB (Bisoprolol, Nebivolol), CCB (Amlodipine), Diuretics (Hydrochlorothiazide – in combination with ACEs or ARBs or BBs).
- 2- The third group is included 48 Hypertensive patients with Diabetes Mellitus (DM) type II (23 men/25 women). They are chronically taking medications from the ACE (Ramipril, Perindopril),



- ARB (Losartan, Irbesartan, Candesartan), BB (Bisoprolol, Nebivolol), CCB (Amlodipine) + Sugar-lowering medications. In view of the poor economic situation that the country is going through, in terms of the high cost of living, new generation of medicines and others, as well as the loss of most medicines during the spread of Corona disease, it was necessary to use cheap medicines from classes of oral antidiabetic drugs (OADs): biguanides (metformin), sulfonylureas (glimepiride), thiazolidinediones (pioglitazone), dipeptidyl peptidase IV inhibitors (sitagliptin).
- 3- After a year of treatment, it was found that the blood pressure had stabilized at the third group, but the blood sugar remained high for some, which necessitated the creation of a new subgroup in this category, where SGLT2 inhibitor (empigliptin or dapagliptin) was added for 1 year.

The group of patients with HTN, after determining the appropriate medications and stabilizing blood pressure, continued to take antihypertensive drugs for two years.

As for the group of patients with HTN associated with DM (Diabetes Mellitus), they started taking appropriate medications for a year until the end of 2021. At the beginning of the new year - 2022, it was necessary to add SGLT2 inhibitors to some patients who did not reach the target in HbA1C, despite the stability of blood pressure.

After a year of treatment, it was found that the group of patients HTN associated with DM had reached its goal in treating DM, but what was remarkable was that it began to suffer from a drop in blood pressure (Hypotension), which necessitated a reduction in the antihypertensive drugs in this group.

After adding these medications, in the fourth group taking SGLT 2, a slight increase in frequency of urination was observed, and patients generally lost some weight (3-4 kg). Also a drop in blood pressure was observed in this group, by more than 20 mm Hg, along with a feeling of hidden dizziness, weakness, and vomiting, which necessitated removing diuretics and reducing the amount of blood pressure-lowering medications.

Dynamics of IMM show an increase in HTN groups compared with the control group.



Methods for improving computer morphometric processing of sections of the rat hippocampus.

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Aim: To study possible options for digital work with research material to improve the quality and speed of work, to create our own software suitable for solving the tasks.

Materials and methods. The study was conducted on microphotographs of hippocampal slices of mature male rats of the Wistar line. Auxiliary programs were also involved in the work: Python 3.8, Cascade trainer GUI, FastStone Image Viewer, Bulk rename utility, Adobe Photoshop CC 2019. During several months of studying Python programming, it was possible to write a neural network capable of distinguishing cells from microphotographs of slices of the hippocampus of rats. Machine learning methods were used in the work. Within a month, we collected a cascade of data containing photos of slices and separately cut neurons. This cascade was later used in training a neural network to recognize the cells we need. After training and tests, the neural network was integrated into the basic interface. The functions of uploading photos and processing them have been added.

Results. In 5 months, we managed to create the necessary program that copes well enough with the tasks set. The program is able to scan the entered photo, find the cells we need on it and mark them with red frames, as well as calculate the total number of objects found.

Conclusion. The result of the work is positive. The neural network works and copes with the tasks quite well, but it requires improvement. Our program successfully detects cells with a probability of 80%. At the moment work is underway to improve the quality of the neural network.



When to Eat, How Often to Eat, What to Eat and How to Eat

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Franz Halberg demonstrated for the first time that eating in the morning causes a decrease in weight, whereas eating same amount of energy in the evening has no influence on body weight. Epidemiological studies indicate that populations of shift workers, in particular those with the consumption of a large percentage of total daily calories after dinner have increased risk of obesity and metabolic syndrome. Previous clinical studies suggest that consuming a majority of daily nutrients in the night may have adverse effects. This review aims to highlight the role of time of eating, food content, way of mastication, and pattern of eating on risk of obesity and metabolic syndrome (MS). Increased intake of Western-type foods characterized with high saturated fat and sugar causes increased oxidative stress, rise in free fatty acids and pro-inflammatory cytokines, which can damage the central circadian clock and peripheral clocks present in liver and adipocyte [1-5]. There is damage to clock genes, which may be associated with increased adipose tissue with altered body fat distribution, such as central obesity, a risk factor for obesity-related disorders [1, 3-6]. Central obesity is associated with MS, which is a risk factor for cardiovascular diseases (CVDs) [4, 5]. Late-night sleep in association with late-night eating further contributes to the development of MS. Emerging evidence from both cell-based and human studies suggests that expression of the circadian clock transcription network within adipose tissue may influence both adipogenesis and the relative distribution of subcutaneous versus visceral depots, Figure 1.

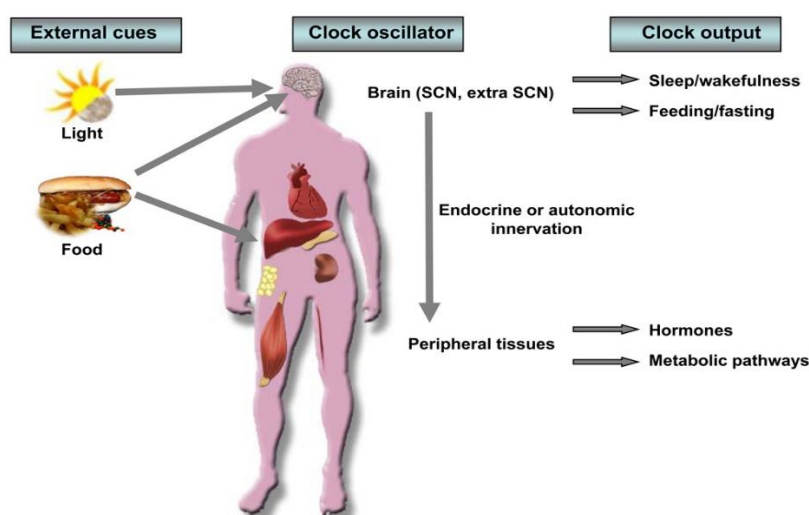


Figure 1. Light and diets as environmental cues, received by the SCN to maintain synchronicity with peripheral clocks in various organs, which may be dysregulated by eating late in the night.

The photic input is transmitted via the retino-hypothalamic tract to activate the SCN, which maintains circadian synchrony of peripheral clocks, a process that involves transmission via both autonomic innervation and/or humoral signals [1-3].



Circadian oscillators may also be entrained by food types, feeding schedule, chewing, late-night sleep and hormone secretion. The core clock machinery has been identified in most peripheral tissues, in association with rhythmic gene expression. However, circadian disruption either within or amongst individual tissues may lead to organ dysfunction. There is increase in ghrelin and cortisol and reduction in leptin and melatonin, which may increase appetite leading to weight gain, obesity and metabolic syndrome. Further studies indicate that peripheral clock alteration is involved in weight gain, glucose homeostasis and blood pressure regulation, thereby contributing to the development of the MS. These alterations may be initiated by disruptions in circadian behavioral and/or environmental factors such as high-fat diet (adverse effects), eating fruits, vegetables and whole grain (protective). Chewing of foods may be an alternative approach to regulate circadian clock function and prevention of MS. In a randomized, crossover trial among 22 subjects, Singh et al. reported that feeding in the evening was associated with significant ($P<0.001$) increase in body weight, body mass index and waist circumference as well as in blood glucose and systolic blood pressure, Table 1.

Table 1. Effect of circadian restricted feeding in the morning or evening on parameters of metabolic syndrome.

Variable	PM (Evening) meal (n=22)	AM (morning) meal (n=22)	Difference (95% CI)
Weight (kg)	62.82 ± 7.45**	62.02 ± 7.52	0.80 (0.53 - 1.06)
Body mass index (kg/m ²)	23.74 ± 2.98**	23.44 ± 2.97	0.30 (0.20 - 0.41)
Waist circumference (cm)	84.45 ± 9.27*	83.32 ± 8.68	1.13 (0.94 - 1.44)
Blood Pressure (mmHg)			
Systolic	113.7 ± 11.2*	112.2 ± 11.6	1.50 (0.17 - 2.92)
Fasting Blood Glucose (mg/dl)	77.95 ± 3.81	74.86 ± 3.67	3.09 (1.63 - 4.56)
HbA1c (% unit)	4.73 ± 0.14**	4.45 ± 0.15	0.28 (-0.23 - -0.33)

Values are mean ± standard deviation, * $P<0.05$, ** $P<0.001$.



Features of the Circadian Profile of Blood Pressure and Heart Rate Under Round-The-Clock Lighting in Spontaneously Hypertensive Rats.

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Background: Round-the-clock lighting, also known as continuous illumination or light exposure during both day and night, has become increasingly prevalent in modern society due to the widespread use of artificial lighting sources. This 24/7 access to light disrupts the natural circadian rhythm, which can have significant implications for human health.

In the conditions of the Far North, people experience extreme variations in natural lighting due to polar day and night phenomena. During the polar day, which can last for several months, there is continuous daylight, while in polar night, there is prolonged darkness.

Research studies have demonstrated that exposure to round-the-clock lighting, especially during nighttime, can lead to disturbances in the body's circadian rhythm. The circadian system plays a crucial role in regulating various physiological processes, including blood pressure. Disruptions in the circadian rhythm, caused by continuous light exposure, may result in abnormal fluctuations in blood pressure [1,2].

Besides its impact on blood pressure, round-the-clock lighting can also influence heart rate. Disruptions to the circadian rhythm and prolonged exposure to light, especially during nighttime, have been associated with alterations in heart rate patterns [3].

Overall, the relationship between round-the-clock lighting and its effects on blood pressure and heart rate highlights the importance of maintaining a regular sleep-wake cycle and minimizing nighttime exposure to artificial light. This is particularly relevant for individuals working in environments with extreme lighting conditions, such as those experiencing polar day and night, as they may be more susceptible to circadian rhythm disruptions and related cardiovascular consequences.

Methods: The experiment was performed on male SHR rats (spontaneously hypertensive rats) and Wistar Kyoto rats (control group). Two light patterns were modeled: 12 hours light / 12 hours darkness (standard light pattern) and 24 hours light without darkness (round-the-clock lighting pattern). The levels of blood pressure (BP) and heart rate (HR) were measured by continuous 24 hour monitoring of these indices by the method of telemetric monitoring using the equipment Data Sciences international (USA). Data were processed using the computer programs: Dataquest A.R.T. 4.2 Gold (USA) and ChronosFit (Germany) [4]. For all indicators the following values were determined by the method of linear analysis: mean 24 h values, daytime and nighttime values of systolic BP, diastolic BP and HR.

Results and Review:

In animals of the control group with round-the-clock lighting, the circadian rhythm of blood pressure (BP) was not detected, only a tendency to an increase in nighttime systolic BP and diastolic BP compared to daytime was noted. A similar pattern was also characteristic of SHR rats,



in which ones blood pressure indicators also did not demonstrate a circadian rhythm either under the standard regimen (12 h : 12 h) or under round-the-clock lighting (24 h : 0 h).

Unlike blood pressure, heart rate is characterized by a distinct circadian rhythm, which persists even in the absence of darkness during the day. Attention is drawn to the fact that in spontaneously hypertensive rats, the heart rate is higher compared to the control group of normotensive animals both during the day and at night.

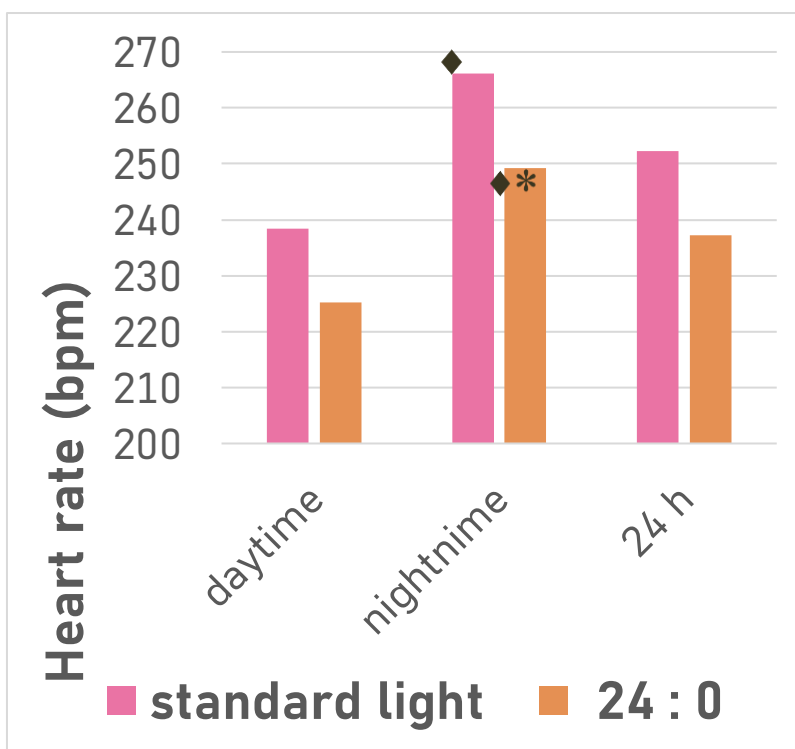
Under conditions of round-the-clock lighting, compared with the standard light regime, in Wistar-Kyoto rats, there is a tendency to a decrease in heart rate in the daytime. At the same time, the difference in HR at night is significant. In hypertensive rats there is a significant decrease in heart rate both during the day and at night. Heart rate retains the circadian structure both under standard lighting conditions and under round-the-clock lighting. Thus, the complete absence of darkness during the day does not affect the HR chronostructure at normal and elevated blood pressure.

Table 1. BP in Wistar-Kyoto and SHR rats under standard and round-the-clock lighting

	Wistar-Kyoto rats		SHR	
	standard light	24 h light	standard light	24 h light
	systolic BP, mmHg			
Daytime	116.54±2.12	111.24± 1.61	191.32±11.47	187.26± 6.37
Nighttime	118.05±2.32	116.11± 3.41	194.68± 8.83	192.64± 4.88
24 h	117.29±2.17	113.67± 2.25	193.00±10.05	189.95± 5.60
	diastolic BP, mmHg			
Daytime	82.74±3.23	82.79± 5.68	131.59± 9.50	138.94± 4.34
Nighttime	84.64± 4.40	87.59± 7.51	135.72± 7.01	141.06± 4.80
24 h	83.69±3.82	85.19± 6.51	133.66± 8.08	140.00± 4.55

Figure 1. HR in Wistar-Kyoto rats under standard and round-the-clock lighting

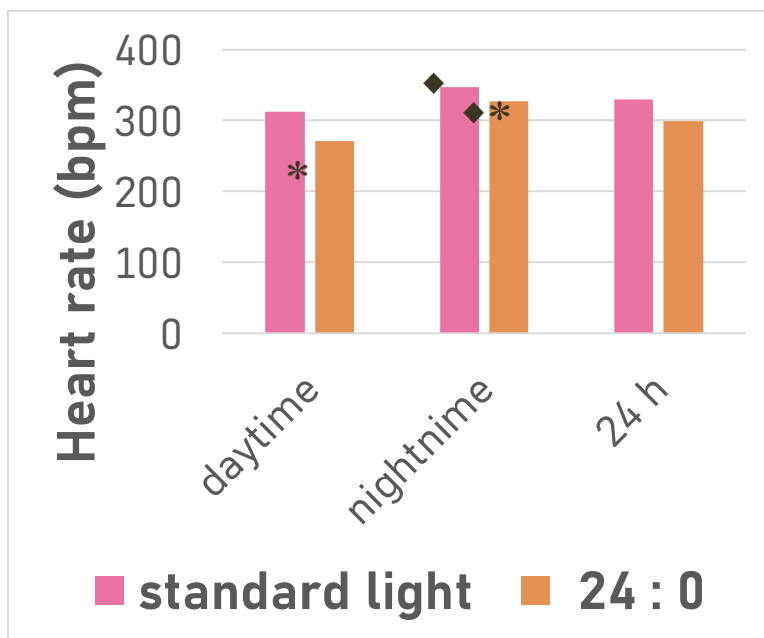




* - $p < 0,05$ data reliably different from the standard light mode

◆ - $p < 0,05$ data significantly different from daily values

Figure 2. HR in SHR rats under standard and round-the-clock lighting



* - $p < 0,05$ data reliably different from the standard light mode

◆ - $p < 0,05$ data significantly different from daily values

Conclusion: Round-the-clock lighting did not lead to a change in blood pressure, while the heart rate decreased significantly, but the circadian rhythm remained.

Keywords: blood pressure, circadian rhythm, cardiovascular disease, light pollution.



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Gene Expression Differences in Peripheral Blood of Patients with Early Stages of Parkinson's Disease.

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Introduction: Parkinson's disease (PD) is a chronic progressive neurodegenerative disease characterized primarily by the death of dopaminergic neurons in the substantia nigra (SN) pars compacta [1]. It has now been shown that the development of the pathologic process in PD may be accompanied by changes in the expression of a number of genes both in the SN and striatum and in other tissues [2]. Published data suggest that blood cells, particularly lymphocytes, may be a model for investigating the processes occurring in the brain in PD [3-7]. The aim of the present work was to study gene expression changes at the transcriptome level in peripheral blood of patients with early stages of PD.

Materials and methods: In this study, we have studied 2 groups of patients with PD (treated and untreated) and 2 comparison groups (neurological controls and healthy volunteers). Analysis of mRNA levels was performed using reverse transcription and real-time PCR with TaqMan probes.

Results: Significant increases in expression in the both groups of patients with early stages of PD (treated and untreated) were obtained for *HNMT*, *NSF*, and *PTGS2* genes. In the group of untreated patients with early stages of PD, a decrease in the expression level of the *MTAI* gene was found. An increase in *ADORA2A* gene expression was observed only in a sample of treated patients with early stages of PD.

Conclusions: Our results suggest that *MTAI*, *PTGS2*, *NSF*, and *HNMT* genes are likely involved in the pathogenesis of early stages of PD and can be considered as potential biomarkers of the disease. Altered expression of the *ADORA2A* gene in treated PD patients may indicate that this gene is involved in processes affected by antiparkinsonian therapy.

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Investigation of the Effect of Decrease Anxa2a Gene Expression on Embryonic Development of *Danio Rerio* Using Morpholino Oligonucleotides

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Introduction: ANXA2 protein encoded by the ANXA2 gene is a member of the annexin family. Protein ANXA2 is involved in many processes, primarily related to cellular transport [1]. Currently available studies of the involvement of ANXA2 in pathological processes are primarily studied the role of ANXA2 in the development of cancer [2]. Impaired functioning of ANXA2 may contribute the development of pathological processes in the nervous system [3]. We find that the ANXA2 gene may be involved in the development of early stages of neurodegeneration [4]. In this study we investigated effect of suppression of *anxa2a* gene expression on the nervous system functioning in the model of *D. rerio* using morpholinos.

Materials and methods: The wild type strain AB of *Danio rerio* was used. Embryos were injected with morpholino to block expression of the *anxa2a* gene. The effect of injected morpholinos to embryonic development was estimated by analysing the change of phenotype at 2 and 4 days post-fertilisation (dpf).

Results: The large number of deformations were observed in both intact and morpholino-injected groups at 4 dpf. These data suggest that the observed deformations are nonspecific. In contrast, at 2 dpf, of the hindbrain ventricular enlargement was observed only in groups injected with morpholinos block *anxa2a* gene expression.

Conclusion: The effects detected at 2 dpf is appear to be specific. Thereby, the most optimal time point for analysis change expression is 2 dpf. The presence of deformations of the hindbrain ventricular may indicate the possible involvement of the *anxa2a* gene on the nervous system dysfunction.

Keywords: *Danio rerio*, nervous system, morpholino oligonucleotides, *anxa2a*, microinjection

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Possibilities of Botulinum Toxin Type a in Reconstructive Surgery of the Anterior Abdominal Wall

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Relevance:

The problem of surgical treatment of patients with postoperative ventral hernias (POVH) W3 remains relevant due to the high risks of complications associated with increased intra-abdominal pressure. Currently, the most commonly used method to reduce intra-abdominal pressure is the technique of mechanical separation of the components of the anterior abdominal wall. [1,2,3] However, such techniques do not restore normal biomechanics of the anterior abdominal wall. In this connection, the most pathologically substantiated method is chemical denervation of the broad abdominal muscles. [4,5]

Materials and methods:

We treated n = 32 patients with PVH with preoperative injection of botulinum toxin type A (BTA) into the vast abdominal muscles, followed by hernioplasty.

Results:

In 78.13% of patients (n=25), it was possible to avoid separation techniques, which made it possible to restore normal biomechanics of the anterior abdominal wall and not cause abdominal compartment syndrome. In 21.88% of patients (n = 7), retromuscular hernioplasty was supplemented with the anterior separation technique according to Ramirez. Wound complications occurred in 37.5% (n=12) of patients. An observation period of 12 months or more did not reveal a relapse of the disease.

Conclusion:

The technique of preoperative injection of botulinum toxin type A into the broad abdominal muscles allows the number of separation techniques to be reduced by 4 times. The relapse-free result is due to the prolonged effect of BTA on the broad abdominal muscles, which contributed to the formation of a denser aponeurotic scar.

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Legal Aspects of Photodynamic Therapy of Malignant Neoplasms

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Malignant neoplasms remain one of the most acute medical and social problems. The contingent of cancer patients is more than 2 million people, that is, 1.4% of the population of Russia. It is especially difficult to help patients who are not subject to radical treatment due to the prevalence of the tumor process or the ineffectiveness of the therapy; with tumors of "inconvenient localization", excluding surgical and/or radiation treatment; due to the refusal of surgical treatment due to the formation of gross cosmetic, sometimes disfiguring defects on the face; which are not subject to radical treatment due to the high risk of intraoperative and postoperative complications due to severe concomitant pathology.

It should also be mentioned the difficulties of providing palliative care in patients of the senile group when it is impossible to carry out special treatment, especially in the presence of bacterial and fungal infections, purulent-inflammatory processes in the area of the pathological focus, severe pain syndrome. Considering these circumstances, the issues of providing real assistance to thousands and thousands of patients and their family members grow into a serious medical, social and humanitarian problem.

One of the most remarkable achievements of fundamental and applied physics of the second half of the twentieth century was the discovery of phenomena that served as the basis for the creation of an optical quantum generator, or laser. In addition to two well-studied and widely used in clinical practice areas of laser application – low-intensity stimulating and high-energy damaging radiation, a third area is rapidly developing – photodynamic therapy of tumors (PDT). The interest in it is due to the fact that selective destruction of the tumor is achieved by irradiating it with low-intensity laser light [1,2], eliminating the danger of uncontrolled thermal damage to the organ wall [3].

In recent years, a new global trend has emerged – a medical technology called photodynamic theranostics. It consists in a comprehensive solution of therapeutic and diagnostic problems by creating drugs that are both a means of early diagnosis and a therapeutic agent [4-6].

Non-adjuvant, intraoperative and adjuvant PDT have become an effective component of the combined treatment of malignant neoplasms, significantly improving the quality, and in some cases, the life expectancy of patients [7-13].

To resolve the issue of conducting PDT as a method of treating an oncological patient, it is necessary to hold a consultation of specialists on the basis of the Order of the Ministry of Health of the Russian Federation Order No. 116n of February 19, 2021 "On Approval of the Procedure for the Provision of Medical Care to the Adult Population for Oncological Diseases", clause 16. The treatment tactics are established by a council of doctors, including oncologists, a radiotherapist, a neurosurgeon (for tumors of the nervous system) of a medical organization that includes departments of surgical methods for the treatment of malignant neoplasms, antitumor drug therapy, radiotherapy (hereinafter referred to as the oncological consultation), including an



oncological consultation conducted using telemedicine technologies, with the involvement, if necessary, of other medical specialists. When changing the method of treatment, an oncological consultation is mandatory. The decision of the oncological council is drawn up in a protocol on paper, filled out legibly by hand or in printed form and signed by the participants of the consultation, or in the form of an electronic document.

A necessary precondition for medical intervention should be filled in by the patient or his legal representative "Informed voluntary consent to medical intervention and refusal of medical intervention" on the basis of complete information provided by a medical professional in an accessible form about the goals, methods of medical care, the risk associated with them, possible options for medical intervention, its consequences, and also about the expected results of medical care ("Law on the basics of public health protection in the Russian Federation No. 323 of 21.11.2011" Chapter 4 of Article 20).

The fields of application of photodynamic therapy are not limited to oncology. In recent years, it has been shown that photodynamic therapy is promising for the treatment of macular degeneration of the retina; psoriasis, rheumatoid arthritis, atherosclerosis, restenosis of blood vessels after balloon angioplasty, periodontal disease, bacterial and fungal infection, as well as for decontamination of transfused blood and its components from viruses. In recent years, PDT has been successfully used for photochemical skin revitalization in cosmetology.

In the Russian Federation, many medical technologies related to PDT are approved by Roszdravnadzor and are a method of combined treatment of malignant neoplasms as part of the provision of high-tech medical care funded from the federal budget or from the Federal Compulsory Medical Insurance Fund. You can get acquainted with the list of these technologies in the Decree of the Government of the Russian Federation dated 29.12.2022 N 2497 "On the Program of state guarantees of free provision of medical care to citizens for 2023 and for the planning period of 2024 and 2025".

Oncological care includes section II "List of types of high-tech medical care not included in the basic program of compulsory medical insurance, financial support of which is provided by subsidies from the budget of the Federal Compulsory Medical Insurance Fund to federal state institutions, subsidies to the federal budget from the budget of the Federal Compulsory Medical Insurance Fund in order to provide subsidies to the budgets of the subjects of the Russian Federation and budget appropriations of budgets of the subjects of the Russian Federation".

Regulatory legal acts defining the rights of cancer patients in the field of drug provision (including photosensitizers) include:

- Federal Law of the Russian Federation No. 323-FZ of November 21, 2011 "On the Basics of Public Health Protection in the Russian Federation";
- Federal Law of the Russian Federation of November 24, 1995 N 181-FZ "On Social Protection of disabled people in the Russian Federation";
- Moscow City Government Resolution No. 3044-PP of December 29, 2022 "On the Territorial Program of state guarantees of free medical care to citizens in the city of Moscow for 2023 and for the planning period of 2024 and 2025";
- Law "On Consumer Rights Protection" dated 07.02.1992 No. 2300-1;
- Federal Law of the Russian Federation of July 17, 1999 N 178-FZ "On State social Assistance";



● Decree of the Government of the Russian Federation of July 30, 1994 N 890 "On State support for development medical industry and improving the provision of medicines and medical products to the population and healthcare institutions".

The procedure for prescribing medications to cancer patients who are not included in the relevant standard of medical care is carried out in accordance with Federal Law No. 323-FZ of November 21, 2011 "On the basics of protecting the health of citizens in the Russian Federation" (paragraph 5 of Article 37), taking into account the decision of the medical commission of the medical organization and the availability of medical indications.

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Processing and Analysis of 3d Images in Biomedical Scanning Probe Microscopy for Clinical Medicine

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In biomedical scanning probe microscopy, data processing and analysis is a key, responsible and very time-consuming process. Viruses, bacteria, cells, living matter and other biological samples are complex objects that require careful handling at all stages of sample preparation, measurements, quantitative analysis, presentation of the results, reporting, preparation of presentations, articles and other illustrative material. For this reason, the software, having all the necessary functions, should have a friendly and intuitive interface.

Recently, using the data of atomic force microscopy of protein nanoparticles as an example, we have shown that for the search for those nanoparticles whose sizes are comparable to the noise level, a more accurate result is given by an algorithm using a neural network [1].

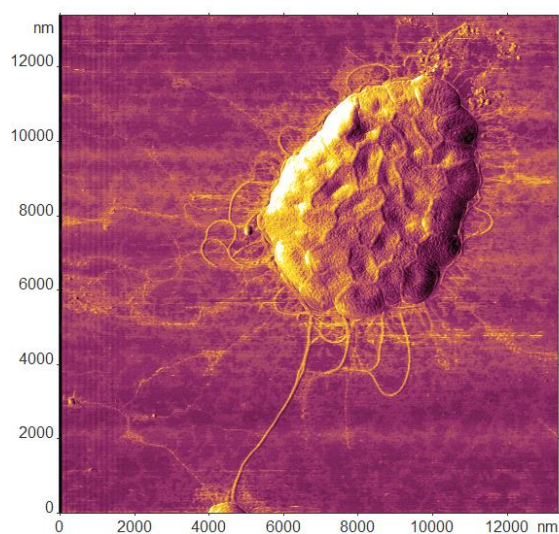


Fig. 1. Image of an islet colony of bacteria *Escherichia coli*.

When visualizing biological objects, for example, *Escherichia coli* bacteria (Fig. 1), in addition to 3D images, you can simultaneously obtain a large array of quantitative data - dimensions, volume, area, contour length, roughness, form factor, coefficients of friction and elasticity, adhesion value. In this case, measurements are carried out on living bacterial cells. Similar multifactorial information can be obtained by studying viruses [2], blood cells, networks of neurons, and various tissues of living organisms.

Modern possibilities for processing 3D images of biomedical microscopy can be easily demonstrated using the example of FemtoScan Online software [3], www.nanoscopy.ru.



Additional features of fast viewing, slideshow, stereo visualization, flying over the surface, rich palette of colors and many other original solutions make FemtoScan Online software comfortable and efficient.

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