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Final Report

"Relevance for healthy food supplement Bio-Normalizer in diet of astronauts, jet pilots and air dispatchers"

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INTRODUCTION

For the enhancement of reliability and stability of the work of human operators under the extremal conditions, it is of importance to enlarge the homeostatic range of physiological functions and latent capacities of an organism. In principle, the correction of the capacity to work and the health conditions of human operators can be achieved by two methods:

(1) The development of specific pharmacological agents.

(2) The development of non-specific pharmacological agents, which activity is practically independent of the nature of extremal factors.

Various food supplements with high biological activity are very perspective non-specific pharmacological agents and, therefore, can be applied for this task. It has been shown in numerous biochemical studies and clinical trials that Bio-Normalizer (BN), a natural Japanese food supplement prepared by the fermentation of *Carica papaya* (Sun-O International, Gifu, Japan), is a powerful immunostimulator and an antioxidant. Therefore, it was supposed that BN might exhibit a favorable effect on the activities of human operators.

The major purpose of present study was to estimate the basic immunobiochemical effects of BN on human operators under hypobaric hypoxia, dynamic physical loading, and the other factors of the aviation flights such as psycho-emotional and audible stress.

1. Basic characteristics of Bio-Normalizer

Previous rehabilitation clinical trials with BN of leukemic patients after radio- and chemotherapy show that its administration led to the improvement of patients' state and mood, an increase in the body weight and motive activity, the normalization of free radical

status of an organism, the enhancement of γ-interferon content in serum, an increase in the phagocytic activity of blood monocytes, and the improvement of liver functions. Similarly, the beneficial effects of BN administration were shown at the treatment of patients with bronchial asthma, allergic dermatitis, virus hepatitis's B and C, and diabetes mellitus. It has been suggested that in all cases the therapeutic effects of BN administration are explained by two reasons: the stimulation of the formation of γ-interferon and the suppression of oxidative stress.

Both mechanisms may be of a great importance for the improvement of the reactions of human operators under the extremal conditions of their professional activity (the changed gas medium, dynamic physical loading, the unfavorable effects of environment, etc.). Therefore, it was supposed that BN administration could have significant beneficial effects on the professional activity of human operators.

HUMAN OPERATORS, MATERIALS AND METHODS

The clinical study design was constructed on the basis of main principles of occupational physiology for military workers, air pilots, cosmonauts and others who are subjected to exposure to stress situations and unfavorable conditions of environment. The study consisted of two stages: (1) The effects of Bio-Normalizer on immune status and biochemical homeostasis; (2) Bio-Normalizer as a protector against stress induced by hostile habitable environment and flying situation.

The general characteristics of the study are presented in Table 1. The experiments were carried out on 18 male healthy volunteers aged from 20 to 35 years after their informed consent. The Military Health Commission admitted all participants to work as military service men, air pilots and cosmonauts after preliminary examination.

The clinical study was a pilot, partly double-blind, randomized trial, in which all participants played roles either control or experimental subjects depending on intake of Bio-Normalizer or placebo powder, which resembled BN in taste and sachet design. The

duration between the control and experimental examinations was not less than 7 days necessary for rehabilitation and restoring the background functional state of the participants. The scheme of BN administration was as following: 2 sachets at bedtime daily for 3 days and 1 sachet 1 hour before physical and psycho-emotional stresses connected with imitation of flying situation. The instrumental and clinical laboratory tests were done 3 times: at the background level, after short-term BN course, and after hypobaric hypoxia, physical and psycho-emotional loading.

The statistical evaluation of the results was performed by t-Student and non-parametric tests assuming $p<0.05$ as a significant level of difference and using "Medical Statistics" software for IBM compatible PC.

The hypobaric hypoxia conditions were created in a training decompression chamber SBC-80 (Russia). Two experiments were performed: Group I, human operators were given BN according to above scheme; Group II, the same participants were given placebo by similar scheme, then, high-altitude endurance was estimated using appropriate physiological parameters such as lung functions, hemodynamics, and mental working capacity. All measurements were done at the hypoxia corresponded to 5 or 6 km of altitude. At the end of 5-min exposure at the 6 km altitude, operators were allowed to inhale oxygen (6 km + O_2) and then were lowered to sea level altitude. Before the altitude ascent, at 5 and 6 km, and at the sea level altitude, the operators were examined by calculation/writing test during 1 min (a consecutive abstraction of 17 from the three-digit figure) and assessed self-account feeling using special score. A severe impairment of mental working capacity (slow-thinking, numerous errors, incapability to make simple calculations) was a signal for clinical investigator to stop further high- altitude ascent. The other symptoms of low hypoxic endurance (bad feeling, respiratory and cardiovascular complications) were assumed as a turning point in the experiments.

The reaction to high-altitude hypoxia from the side of cardiovascular system was assessed by monitoring of electrocardiography, blood pressure, rheography, systolic and minute circulating blood volumes, blood output rate, and peripheral vessel resistance. Before the altitude ascent and immediately after lowering, the lung functions, dynamometric measure of hand and static muscle endurance were determined.

To assess the physical working capacity, the veloergometry test was used on a "Ergo-line 900" veloergometer (Germany). The physical loading increased gradually by 25 W/min starting from 50 W up to critical values of blood pressure, heart rate, and electrocardiography.

The respiratory functions and gas/energy metabolism were studied on a spiroergometry system 2900 (SensorMedics, USA). An exhaled air was analyzed by mass-fluorometric method. The partial pressure of oxygen and carbon dioxide in an exhaled air was measured breath by breath using zirconium and infrared sensors. The partial pressure of oxygen and carbon dioxide in tissues was measured by a Radiometer monitor (USA) transcutaneously. An anaerobic threshold was measured by V-slop method. All laboratory and instrumental tests were performed in the morning before breakfast.

Total, 128 primary and calculated parameters were determined to characterize the functional state of the lungs, cardiovascular system, and tissue respiration and metabolism.

To determine immunological and biochemical parameters the venous and capillary blood and urine were used. Blood serum was obtained by standard procedures, and levels of total and α-cholesterol, triglicerides, glucose, creatinine, urea, and uric acid were measured by spectrophotometric method on a clinical laboratory analyzer (Labsystem, Finland). The activities of intracellular enzymes such as lactate dehydrogenase (LDG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPC), γ-glutamyltransferase (γ-GT), and acid and alkaline phosphatases were measured by conventional methods on the same analyzer.

The content of immunoglobulin G, M, and A was measured using Manchini method. The lymphocyte subpopulations were detrmined using monoclonal antibodies.

The parameters of blood coagulation were measured by conventional laboratory tests. To evaluate the osmotic resistance of erythrocyte membrane, the number of cells with low resistance, time of hemolysis, and functional activity of erythrocytes were determined. B-adrenal receptors on the surface of erythrocyte membrane were studied using obzidane hemolysis.

The effects of BN on psycho-physiology of human operators in the hostile habitable environment were determined in a training chamber imitating the fighter cabin (low volume

hermetic cabin, acoustic noise, catapult chair with safety belts, protective helmet, and oxygen mask). The training chamber allowed imitating the different kind of pilot work. Four operator tests of different complexity were used: (1) the three-choice reaction to the colored lamp flash, which was performed for 3 min; (2) the two-choice reaction to digits, which was performed for 3 min; (3) two-dimensional compensatory eye-movement for light signal of 0.15 Hz frequency during 5 min; (4) eye-movement plus two-choice reaction during 5 min. As the parameters of mental working capacity we used a number of total answers, a number of right answers, a number of errors, the rate of information consumption, efficiency coefficient ($K = 1 - T/8$, where T is the time of errors, sec).

To assess the psycho-functional state of human operator the following characteristics were determined: (1) triad of self-account feeling + activity + mood; (2) the situation and personal anxiety according to Spilberg score; (3) pulse rate monitored by a "Physiologist-M" counter.

RESULTS

1. Effects of Bio-Normalizer on immuno-biochemical status of human operators.

The main aim of this part of clinical study was to elucidate the effects of Bio-Normalizer on metabolic processes and immune reactivity of the organism. The results are presented in Tables 2-7. Table 2 shows that BN administration leads to statistically significant elevation of hemoglobin concentration (+8%, $p<0.05$). These data could be interpreted in terms of epigenomic induction of protein synthesis by BN as it was a short-term BN administration course. It seems to be very likely that prolongation of the therapeutic course would be helpful to distinguish the genomic and epigenomic effects of BN on protein synthesis. BN affected to a large extent the blood eosinophil and monocyte counts (Table 2) inducing the monocyte subpopulation (+101%, $p<0.05$) and suppressing the eosinophil one (-61%, $p<0.05$). Obviously, these effects could be regarded as those of utmost clinical importance

because they reflect the cellular immune reaction, which increases the body tolerance towards unfavorable external invasions.

The erythrocyte functions were assessed by means of their osmotic resistance and number of β-adrenal receptors on erythrocyte membrane (Table 4). There were no significant changes in the mean values of both parameters. This allowed us to suggest that under the experimental conditions BN did not affect either membrane resistance or adrenal system. However, we observed the individual reactions to short-term BN administration. Thus, a number of β-adrenoreceptors on erythrocyte membranes of two male operators was found increased. Another evidence of the adrenal system activation by BN was gathered from the results presented in Table 5. It was found that BN increased significantly the catecholamine excretion with urine. The excretion of noradrenalin increased by 33%, $p<0.05$ and adrenalin by 8%, $p<0.05$. These data point out to anti-stress properties of BN, to its capability of mobilizing the main adaptive systems and increasing the self-protection of the body.

The anti-stress properties and mobilizing capacity of BN were proven again by the dinamics of intracellular enzymes in blood serum (Table 3). It was shown that BN administration led to release aspartate aminotransferase (+26%, $p<0.05$), alanine aminotransferase (+25%, $p<0.05$), lactate dehydrogenase (+24%, $p<0.05$), and creatine phosphokinase (+38%, $p<0.05$). At the same time, activities of these enzymes remained in the normal range of values. On the basis of these facts, we concluded that elevated levels of intracellular enzymes in blood serum appear to reflect the adequate adaptive reaction of organism to stress conditions but not the cytotoxic effects of food additive studied.

The course of BN administration to human operators did not affect levels of lipids, glucose, urea, uric acid, and creatinine in the blood (Table 5). However, the slight decrease of α-cholesterol (-6%, $p<0.05$) and increase of atherogenity coefficient (+15%) were observed. At the same time, all the parameters of lipid metabolism remained in the normal range of values, therefore BN can not be considered as atherogenic agent.

The effects of BN on the blood coagulation are shown in Table 6. It is quite clear that BN had no any negative effects. It increased significantly the level of fibrinogen (+22%, $p<0.05$) that reflected the enhanced protein synthesis in the liver. All the other insignificant changes might be a kind of adaptive reaction in the complex coagulation system.

The study of immune status revealed the potent immunomodulating activity of BN especially towards T-lymphocytes (Table 7). The CD8+ subpopulation of T-lymphocytes(T-suppressors) increased by 30%, $p<0.05$ and CD4+ subpopulation (T-helpers) decreased by 11%, $p<0.05$. Due to that, the ratio CD4+/CD8+ decreased by 30%, $p<0.05$. This may be explained by adaptive reaction of cellular immune system to hostile environmental conditions directed to improve the organism's self-defensive capacity. The BN application caused the increase of IgA level in the blood that apparently allowed to protect organism against microbial invasion.

On the grounds of the results obtained in this part of study we concluded that

- BN is an anti-stress adaptogen capable of activating the protein synthesis, energy metabolism and enzyme release as well as mobilizing the body reserves.
- BN is a potent immunomodulator acting mainly towards T-lymphocyte and monocyte/macrophage systems.

2. Effects of Bio-Normalizer on endurance to hypobaric hypoxia by human operators.

'A high-altitude hypoxia causes the main health problems for pilots and astronauts. The hypobaric hypoxia affects a lot the mental and physical working capacity of human operators, which very often creates the critical situations during the flight. Therefore experts in the aerospace biology and medicine have been looking for pharmaceuticals capable of ameliorating the adverse effects of high-altitude hypoxia and increasing the organisms' endurance to hypoxic conditions. A proper pharmacological correction of negative hypoxic effects might be also of great importance in the case of aerodrome localization very high in the mountains as well as during the flights with a limited oxygen supply. The main goal of this part of the clinical study was to evaluate the safety and anti-hypoxic efficacy of BN. The comparative data on effects of BN and placebo are gathered in Tables 8A, 8B, 9A and 9B. As a whole, BN did not affect the endurance of human operators to hypoxia at the altitudes 5 and 6 km. However, the effects of BN and placebo on a variety of hemodynamics parameters such as heart rate (+9+21 beat/min), blood pressure, systolic and minute volumes, and peripheral vessel resistance were undistinguished. We also failed to find out any differences between BN and placebo in effects to mental working capacity which was assessed by the calculation/writing test (Tables 9A and 9B).

The self-account feelings of the participants of experimental and control groups at the "5 and 6 km of altitude" were statistically undistinguished (Tables 9A and 9B). There were no differences in dynamometry of hand and static muscle endurance between two groups studied. The mean value of inspiratory apnoea increased up to 5-6 sec in the experimental group, that could be explained by the organisms' urgent adaptation to acute hypoxia.

There were no emergent situations associated with high-altitude decompression illness therefore we concluded that BN did not provoke the high-altitude associated health problems. According to these results BN cannot be regarded as anti-hypoxic agent.

3. Effects of Bio-Normalizer on the endurance to dynamic physical loading.

The effects of BN on muscular energy were studied under normal conditions as well as upon dynamic physical loading by means of veloergometry. It was found that BN administration resulted in significant changes of energy-consuming metabolic processes. Thus, the carbohydrate metabolism increased from the background level 24.4% up to 34.7%. Along with that the suppression of lipid metabolism occurred (from 50.2% to 39.0%). The higher background level of lipid component ("lipid shift") in energy supply of organism was, the more significant "anti-lipid" effect of BN occurred. There were no changes in protein metabolism upon BN challenge. The energy consumption in the normal conditions did not change after BN administration. The effects of BN on hemodynamics of human operators were as following: the minimal and middle values of blood pressure and minute circulatory volume increased and systolic pressure and peripheral vessel resistance decreased. This might reflect the positive effects of BN on the chronotropic function of the heart that is the main way to increase total cardiac output and decrease vessel resistance.

To assess physical working capacity of participants, the maximal blood pressure, heart rate, electrocardiography shifts, and fatigue score by RPE-method (rate perceived exertion) were determined. The maximal bearable loading level was 213±7 W before BN and 220±9 W after BN administration (The changes of mean values were statistically insignificant, $p>0.05$). However, according to RPE self-account score (14.3±1.3 in the

presence of BN *vs* 17.3±0.7 without BN) Bio-Normalizer diminished substantially the post-exposure muscle fatigue associated with physical overload.

The BN application to operators under extensive physical load did not show any significant effects on the lung functions (Maximal respiratory volumes 62.6±4.8 *vs* 63.2±7.8 L/min; FEV1 2.4±0.3 *vs* 2.1±0.2L; Respiratory rate 27±1.2 *vs* 30±1.8 min^{-1} with and without BN, respectively). The respiratory reserve comparing with maximal respiratory volume tended to decrease and was equal 55% of maximal value. The ratio of oxygen/carbon dioxide exchange was found ten-fold higher under physical loading than under normal conditions and did not depend on BN presence. The anaerobic threshold was equal 16.9±0.8 and 16.1±0.7 mL/kg/min; the energy-consuming efficacy of the work was found 11.6±0.5 and 11.7±0.3 mL/min/W that corresponded to the efficiency of the muscle work 24.3±1.0% *vs* 24.0±0.6% with and without BN, respectively. The most important BN effect on the energy metabolism was found from the elevated level of anaerobic energy production (22.7±4.2% *vs* 16.6±2.5% with and without BN, respectively). Examining the Robinson index, we found that BN did not affect the oxygen consumption by myocardium (26.6±2.4 vs 27.7±3.0 with and without BN, respectively).

The muscle-working overload was accompanied by the characteristic sharp increase in the hemodynamic parameters such as heart rate corresponding to 80% of "pulse reserve" (77.0±4.0% *vs* 79.8±4.6% with and without BN, respectively); oxygen pulse dynamics (17.5±1.4 beat/min *vs* 15.7±1.7 beat/min with and without BN, respectively); and the oxygen arterial/venous difference (145.3±3.4 mL O_2/L *vs* 135.3±4.4 mL O_2/L with and without BN, respectively).

The analysis of the data obtained allowed us to make the next conclusions:

1. BN normalizes the energy metabolism decreasing its "lipid component" and subsequently increasing "carbohydrate component". As a consequence, it results in increased efficiency of energy consumption.
2. BN induces the adequate adaptive reactions to physical overload from the side of cardiovascular system such as increased heart rate, minute cardiac output, and blood pressure and decreased resistance of peripheral blood vessels.
3. In response to physical overload, BN induces the adaptive response of the lungs increasing respiratory rate.
4. In general, the energy metabolism is more effective in the presence of BN because of decreased level of energy consumption and increased capacity of anaerobic sources of energy.

4 The effects of Bio-Normalizer on psycho-physiological conditions of human operator in hostile habitable environment

Six healthy male volunteers were studied under normal and unfavorable conditions such as the acoustic noise, the uncomfortable protective equipment, and the intensive activity. Analysis of the parameters of psycho-physiological conditions of volunteers before the BN administration showed that the uncomfortable conditions led to the change of some important parameters in comparison with those measured under normal conditions. For example, a small increase in the heart activity and frequency of cardiac contractions accompanied by some increase in the velocity of information input and a decrease in the sum of mistakes done during the choice of two or three alternatives. In accord with the Medvedev's hypothesis (1979), it may be suggested that these changes in volunteers'

conditions are adaptive ones and can be regarded as an unfavorable factor at the hygienic estimate of the action of various environmental parameters and intensive informative load on the functional activity of a human operator. That suggestion was confirmed by the data obtained during the monitoring on a test-stimulator. Thus, it was found that the time of parrying of erroneous actions increased by 15-20% and the efficacy coefficient decreased by 50-55% under unfavorable environmental conditions.

Before the beginning of the administration of BN to volunteers, it has been ascertained that taking 5 BN sachets during 3 days resulted in no adverse effects in all of them excluding one person who had a heartburn. On the whole, it was found that after BN administration volunteers felt better, manifested the enhanced activity and mood, and increased their capacity for work (Tables 10-13). As is seen from Tables 10, 11, the self-accounting feeling and mood were improved by about 0.6 score and 0.84 score, respectively, for the volunteers in comfortable conditions and by 0.44 score and 0.56 score for the volunteers in the hostile environment. At the same time, the administration of 5 sachets of BN practically did not change the parameters of personal and situation-reactive anxiety as well as the activity of human operators. It is important to stress that although the frequencies of cardiac contractions were high enough for human operators under both favorable and unfavorable conditions (85.4±7.1 and 90.3±6.6 strokes/min, respectively), BN administration resulted in the additional enhancement of this parameter (about 5-7 strokes/min). This fact apparently indicates the enhancement of physiological expenditure of the capacity for work under unfavorable conditions.

Improving the self-accounting feeling and mood and an increase in the frequencies of cardiac contractions after the BN administration were accompanied by the enhancement of

the capacity for work of volunteers under both favorable and unfavorable conditions (Tables 12, 13). As is seen, all the principal parameters improved for 4 volunteers, 2 parameters improved in the case of 2 persons, and no improvement was observed for one person only. Analysis of the capacity for work showed that after BN administration the sum of errors decreased by 15-20% and 30-40% in the case of a choice of two and three alternatives, respectively. On a whole, it was found that BN administration improved the parameters characterized the quality of eye-movement under the favorable and unfavorable conditions such as the time of the correction of errors (up to 25%), a decrease in their sum (up to 60%), and an increase in the efficacy of monitoring (up to 90%). Similarly, the improvement was observed for the parameters of a complex activity under favorable and extremal conditions: the time for parrying of erroneous actions decreased by 25-35%, their sum decreased by 15-20%, while the integral factor of main (monitoring) and additional (a choice from two alternative) task determined as the efficacy coefficient increased by 30-40%.

Thus, BN administration did not affect the subjective estimate of the volunteers' conditions but improved the health conditions and mood and increased the frequency of cardiac contractions. At the same time, there was an improvement of practically all parameters showing the positive effect of BN administration on the working capacity of 67% human operators under both favorable and unfavorable conditions.

Conclusion: In our opinion, the important results obtained should be confirmed in the subsequent trial where the duration of BN administration is to be extended up to 10-12 or even more days with an increased number of volunteers having a low endurance to stressful conditions.

GENERAL CONCLUSIONS

1. BN is an anti-stress agent directed to improve the organisms' adaptation to high-altitude hypoxia, psycho-emotional stress associated with a flying situation, and stress induced by physical overload.
2. At the cellular and metabolic levels, BN activates the energy metabolism, protein synthesis, and the T-lymphocyte and macrophage/monocyte chains of body's immunity.
3. The short-term course of BN administration induces beneficial effects from the lungs and cardiovascular system including increased respiratory and heart rates, minute circulatory blood volume, and arterial blood pressure as well as decreased resistance of peripheral vessels. All these changes reflect the adequate functional response to external stress conditions.
4. Under exposure to physical loading, BN administration increases efficiency of energy metabolism, improves lipid metabolism and induces the elevation of anaerobic sources to the energy metabolism.
5. BN insignificantly improves the self-estimated feelings and mood of human operators in hostile habitable environment, which was reveled by the inquiry tests.
6. The short-term course of BN administration reveals positive effects on the working capacity of human operators (67%) under both normal and stress conditions associated with hostile environment and information overload.
7. All the data obtained should be considered as preliminary ones because the effects need to be further investigated with different schemes of BN administration

(Extension of BN course up to 12-14 days is strongly recommended!) and human operators with high susceptibility to emotional and physical stresses associated with flying situation.

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Table 1. General characteristics of clinical trial.

Clinical laboratory study	Number of participants		
	Experimental group	Control group	Total number
Effects of Bio-Normalizer on immuno-biochemical status of human operator	6	-	6
Effects of Bio-Normalizer on the dynamic physical stress endurance	6	6	12
Effects of Bio-Normalizer on psycho-physiology of human operators under hostile habitable environment	6	6	12
Total number	18	12	30

Table 2. Effects of Bio-Normalizer on hematological parameters of human operators.

Parameter, units	Background level	After BN course
Hemoglobin, g/L	150.80±7.48	163.30±3.02*
Erythrocytes, 10^{12}/L	4.62±0.11	4.67±0.11
Leukocytes, 10^{9}/L	7.08±0.71	6.62±0.71
Polymorphonuclear leukocytes, %	49.87±1.91	52.55±4.57
Eosinophils, %	3.83±0.48	1.50±0.29*
Monocytes, %	4.67±0.42	9.40±0.87*
Lymphocytes, %	41.7±1.78	40.0±4.03

* - $p < 0.05$

Table 3. Effect of Bio-Normalizer on the activities of enzymes in blood serum of human operators.

Parameter, units	Background level	After BN course
Alanine aminotransferase, ALT, U/L	0.28±0.006	0.35±0.04*
Aspartate aminotransferase, AST, U/L	0.43±0.02	0.54±0.06*
Alkaline phosphatase, U/L	2.31±0.23	2.30±0.19
γ–glutamyltransferase, γ-GT, U/L	0.48±0.14	0.47±0.10
Creatine phosphokinase, U/L	1.37±0.20	1.89±0.50*
Lactate dehydrogenase, U/L	2.72±0.09	3.36±0.33*
Acid phosphatase, U/L	2.03±0.26	2.13±0.23

* - $p < 0.05$

Table 4. Effects of Bio-Normalizer on the osmotic lysis and adrenoreceptors of erythrocytes.

Parameter, units	Background level	After BN course
Osmotic hemolysis, absorbance units	0.76±0.13	0.76±0.11
β-adrenoreceptors on erythrocyte membrane, arb. units	16.2±4.73	17.6±4.71

Table 5. Effects of Bio-Normalizer on biochemical parameters in the blood of human operators.

Parameter, units	Background level	After BN course
Cholesterol, μmol/L	7.12±0.50	7.23±0.48
α-Cholesterol; μmol/L	2.08±0.22	1.96±0.20
Atherogenicity Coefficient, arb. units	2.76±0.45	3.18±0.65
Triglicerides, μmol/L	0.97±0.08	1.10±0.23
Glucose, μmol/L	5.75±0.20	5.53±0.37
Urea, μmol/L	5.51±0.50	5.24±0.22
Uric acid, μmol/L	426.6±14.34	459.4±17.08
Creatinine, μmol/L	77.6±2.63	79.7±3.94
Diene conjugates, nmol/mL	0.033±0.014	0.022±0.007
Shiff products, nmol/mL	5.48±1.10	6.65±0.47
Glutathione peroxidase, U/ mg Hb	10.3±1.2	9.9±1.2
Adrenalin, nmol/h	4.25±0.92	4.60±0.89
Noradrenalin, nmol/h	0.52±0.17	0.69±0.19*

* - $p < 0.05$

Table 6. Effects of Bio-Normalizer on blood coagulation of human operators.

Parameter, units	Background level	After BN course
Fibrinogen, g/L	2.96±0.08	3.54±0.15*
Thrombin time, sec	9.67±0.71	9.50±0.43
Recalcification time, sec	202.5±34.76	167.5±16.57
Prothrombin time, sec	22.2±1.38	21.80±0.83
Prothrombin index, %	101.3±6.12	101.7±3.87
Thrombotest, arb. units	5.25±0.31	5.42±0.24
Coagulation of euglobin, sec	67.5±11.15	73.0±7.83
Lysis time of euglobin, min	180.8±16.90	192.5±12.29

* - $p < 0.05$

Table 7. Effects of Bio-Normalizer on the immune status of human operators.

Parameter, units	Background level	After BN course
Active T-lymphocytes, %	65.8±3.52	62.5±4.23
Total T-lymphocytes, %	57.5±3.82	56.7±4.41
CD4+, %	57.5±4.43	51.7±3.80*
CD8+, %	8.33±1.67	10.83±2.39*
CD4+/CD8+	8.67±1.89	6.08±1.27*
IgG, mg/mL	10.4±1.67	9.9±0.58
IgA, mg/mL	1.17±0.15	1.47±0.39*
IgM, mg/mL	2.00±0.34	1.92±0.32
Circulating immune complexes, abs. units	64.2±9.44	40.8±3.96*

* - $p < 0.05$

Table 8A. Effects of Bio-Normalizer on hemodynamics of human operators in the altitude training chamber.

Parameter/ Altitude, km	Sea level altitude	5 km	6 km	6 km + O_2	Ground level
Heart rate, beat/min	71±2.2	80±5.6	91±4.8*	76±4.9	70±4.9
Blood pressure, mm Hg					
max	116±2.4	110±5.7	116±7.0	114±4.6	118±4.6
average	80±2.7	82±4.9	75±4.7	87±3.0	84±4.6
min	54±1.9	54±3.7	52±5.1	61±4.0	61±2.4
Cardiac output, systolic volume, mL	58±3.8	59±3.1	57±4.2	55±3.1	56±4.3
Cardiac output, minute volume, L/min	4.1±0.2	4.7±0.3	5.2±0.4*	4.2±0.2	3.9±0.3
Volume rate of cardiac output, mL/sec	231±12	243±13	246±18	222±8.7	219±15
Peripheral vessel resistance, din/sec x cm	1566±41	1438±168	1213±158	1760±138	1790±188

* -$p < 0.05$

Table 8B. Effects of placebo on hemodynamics of human operators in the altitude training chamber.

Parameter/ Altitude, km	Sea level altitude	5 km	6 km	6 km + O_2	Ground level
Heart rate, beat/min	77±4.0	88±5.6	98±6.5*	78±5.4	73±2.9
Blood pressure, mm Hg					
max	131±3.7	123±4.1	128±2.5	124±1.9	124±5.3
average	88±4.1	88±1.2	80±2.0	91±1.9	87±2.0
min	57±3.7	53±2.0	50±2.0	54±1.2	56±2.9
Cardiac output, systolic volume, mL	69±9.8	71±5.5	65±6.6	65±3.7	64±5.9
Cardiac output, minute volume, L/min	5.3±0.8	6.2±0.5	6.4±0.7	5.1±0.5	4.7±0.4
Volume rate of cardiac output, mL/sec	282±41	305±24	311±28	264±17	256±24
Peripheral vessel resistance, din/sec x cm	1486±275	1200±91	1206±93	1506±165	1537±141

* - $p < 0.05$

Table 9A. Effects of Bio-Normalizer on general conditions, mental and physical capacities, and apnoea of human operators in the altitude training chamber.

Parameter/ Altitude, km	Sea level altitude	5 km	6 km	6 km + O_2	Ground level
Calculations/ Writing capacity					
Number of calculations	13.8±1.8	12.2±2.0	9.8±1.3	12.2±2.3	14.2±2.3
Number of errors	0	0.4±0.4	0.4±0.2	0.8±0.4	0.2±0.2
General conditons, score	4.8±0.2	4.4±0.3	3.9±0.4	4.5±0.3	4.7±0.2
Dynamometric measure (DM) of hand, kg/cm^2	1.0±0.1	-	-	-	1.0±0.1
Static muscle endurance					
75% DM, kg/cm^2	0.75±0.1	-	-	-	0.75±0.1
time, sec	43±10	-	-	-	47±8
Inspiratory apnoea, sec	76±7	-	-	-	79±5

Table 9B. Effects of placebo on general conditions, mental and physical capacities, and apnoea of human operators in the altitude training chamber.

Parameter/ Altitude, km	Sea level altitude	5 km	6 km	6 km + O_2	Ground level
Calculations/ Writing capacity					
Number of calculations	12.2±2.0	11.8±1.8	10.8±1.3	12.2±2.0	13.6±2.1
Number of errors	0.2±0.2	0.2±0.2	0.4±0.2	0.6±0.4	0±0
General conditons, score	4.9±0.1	4.4±0.3	4.1±0.4	4.4±0.2	4.7±0.2
Dynamometric measure (DM) of hand, kg/cm^2	1.0±0.1	-	-	-	1.0±0.1
Static muscle endurance					
75% DM, kg/cm^2	0.75±0.1	-	-	-	0.75±0.1
time, sec	46±7	-	-	-	51±11
Inspiratory apnoea, sec	74±9	-	-	-	80±5

Table 10. Effects of Bio-Normalizer on psycho-physiological state of human operators under normal conditions.

Parameter	Before BN administration	After BN administration
General conditions, score	4.84±0.45	5.44±0.44
Activity, score	5.04±0.47	5.24±0.49
Mood, score	4.92±0.44	5.76±0.40
Situation anxiety,score	36.2±0.8	35.0±1.4
Personal anxiety, score	37.0±4.0	37.3±3.4
Pulse rate, beat/min	85.4±7.4	91.0±5.3

Table 11. Effects of Bio-Normalizer on psycho-physiological state of human operators in flying situation.

Parameter	Before BN administration	After BN administration
General conditions, score	5.12±0.54	5.56±0.49
Activity, score	5.60±0.58	5.48±0.55
Mood, score	5.12±0.46	5.68±0.46
Situation anxiety,score	33.4±1.9	32.2±2.0
Pulse rate, beat/min	90.3±6.6	93.0±5.0

Table 12. Effects of Bio-Normalizer on mental working capacity of human operators under normal conditions.

Parameter	Before BN	After BN	Deviation, %
Three-choice reaction to figures			
Total answers	65.4±3.3	69.1±3.7	+6
Right answers	65.3±3.4	67.6±3.5	+4
Errors	2.2±0.3	1.5±0.6	-32
Information consumption	1.53±0.10	1.67±0.90	+9
Two-choice reaction to figures			
Total answers	55.4±3.8	55.9±3.9	+1
Right answers	53.4±3.8	54.3±3.7	+2
Errors	2.1±0.3	1.6±0.5	-24
Information consumption	0.735±0.039	0.780±0.053	+6
Figure monitoring			
Time of errors	3.9±1.9	3.9±1.7	0
Number of errors	9.0±3.1	3.2±0.1	-64*
Efficiency coefficient	0.51±0.23	0.51±0.21	0
Complex arithmetical exercise			
Time of errors	6.5±2.8	4.1±1.6	-37
Number of errors	14.2±4.8	11.3±3.7	-20
Efficiency coefficient	0.34±0.20	0.51±0.12	+50

Table 13. Effects of Bio-Normalizer on mental working capacity of human operators in flying situation.

Parameter	Before BN	After BN	Deviation, %
Three-choice reaction to figures			
Total answers	68.1±2.6	67.6±3.7	-1
Right answers	66.8±2.8	67.2±3.7	-1
Errors	1.5±0.5	0.8±0.2	-47
Information consumption	1.65±0.09	1.70±0.10	+3
Two-choice reaction to figures			
Total answers	55.8±3.8	57.1±4.2	+2
Right answers	54.4±3.6	55.8±4.1	+3
Errors	1.5±0.2	1.3±0.4	-13
Information consumption	0.742±0.070	0.822±0.070	+11
Figure monitoring			
Time of errors	4.8±2.4	3.6±1.3	-25
Number of errors	11.0±4.1	10.4±3.1	-5
Efficiency coefficient	0.29±0.30	0.55±0.20	+90
Complex arithmetical exercise			
Time of errors	5.9±2.4	4.5±1.6	-24
Number of errors	13.6±4.2	11.5±3.5	-15
Efficiency coefficient	0.39±0.17	0.50±0.13	+28