Clinical Efficacy and Safety of Bio-Normalizer in Management of the Chernobyl Disaster Liquidators

Final Report

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ABSTRACT

Two-centered double-blind case controlled clinical trial have been performed to elucidate both the clinical effectiveness and safety of short-term administration of Bio-Normalizer (BN), a healthy food supplementation, to the Chernobyl disaster liquidators.

Eighty-six patients who suffered the late effects of radiation exposure have been admitted in hospitals and randomized into control and experimental groups. Patients of the experimental groups were given different dosages of BN daily for 1 month along with conventional therapy. The results obtained have shown a complete safety of BN administration that followed from patients' good tolerability, absence of adverse effects, and functions of living important organs such as liver, kidney, and hematopoietic system. Though BN is enriched with natural carbohydrates, it did not affect either the patients' blood glucose level or their tolerability to glucose.

On the biochemical level, BN administration improved significantly the patients' impaired free radical status by decreasing intensity of lipid peroxidation and increasing the reduced glutathione level, the total antioxidant capacity of plasma and the activities of the main antioxidant enzymes.

The positive clinical effects have been found with respect to blood hypertension, some cardiac functions, immune and psycho-neurological status. According to subjective patients' and physicians' observations, the general clinical conditions and quality of life have been improved substantially.

On these grounds, it was concluded that BN could be applied to people subjected to therapeutic, accidental, or environmental irradiation to prevent and cure irradiation-induced free radical-mediated pathologies.

INTRODUCTION

All the world is aware of the atomic bombings of Hiroshima and Nagasaki in 1945, which killed hundreds of thousands of people and left many more who suffered from radiation sickness. Since that several nuclear disasters have occured around the world that resulted in the countless victims and ongoing contamination of the global environment. At this time, there are two major sources of nuclear contamination: nuclear plant accidents, such as the one at the Chernobyl atomic power station on April 26, 1986, and nuclear tests, such as those conducted for many years in Nevada in the United States, Semipalatinsk in Kazakchstan, and Bikini Atoll and other islands in the Pacific Ocean.

According to different sources, at Chernobyl, the total amount of radioactivity present at the time of explosion is estimated from 12 million to 50 million or even as much as 120 million curies (Ci). The spewed radioactive material was mostly composed of cesium-137 (half-life: 30 years), strontium (50.4 days), iodine-131 (8 days), and plutonium (6,600 years). Though both in Chernobyl and Hiroshima, the power of explosions was tremendous, but unlike Hiroshima, mostly the Chernobyl power station personnel, firemen, and soldiers were the ones who suffered from the acute radiation injury, immediate death and late radiation sickness. The largest propotion of the irradiation exposure to men arose from the Cs-137 radionuclide as a result of exposure both to external radiation from surface contamination and internal radiation from consumed contaminated food.

More than half a million of soldiers, firemen, engineers and workers participated in the liquidation of consequences of the Chernobyl catastrophe. Practically all of them have been subjected to the external and internal irradiation for a long time. Some of these people developed the definite clinical features of radiation sickness such as polycytopenia, bone

marrow failure, bleeding, polyarthritis, lung fibrosis, increase of the tumor incidence, and so on. Evidently, mean life span in this human population became significantly shorter than an average one for a whole male population in Russia. At the same time, it became clear that low-level but continuous ionizing irradiation exposure caused several pathological states that have not been described yet as irradiation-induced damage. For example, liquidators likewise aged subjects are subjected to frequent bacterial and viral infections, they exhibited pronounced degeneration of central nervous system, suffered from atherosclerosis,and so on. It has been recently concluded that low-level irradiation induced the premature aging processes in humans. One of the working hypothesis for irradiation-induced ageing is inefficiency or lack of feedback control resulting in the oxidant/antioxidant imbalance in an organism. It is now well established that damaging effects of radiation are mediated by the active oxygen species formed as a result of the direct interaction of γ - and β -rays with the molecules of oxygen, water, and organic compounds. Moreover, incorporated radioisotopes may influence the endogenous systems producing active oxygen species, for example, blood leukocytes, which is thought to be a main source of these species. These species (the inogranic radicals superoxide ion and hydroxyl radical, oxygen-centered organic radicals, and hydrogen peroxide) are able to interact practically with all important biological substances (lipids, proteins, nucleic acids, polysaccharides etc.).

As radiation has always been the part of environment, human beings are adapted in some way to the potential risk of irradiation. There are powerful antioxidant systems in human organism, which protect the cells and non-cellular material against free radicals. They consist of enzymes such as superoxide dismutases (SOD), catalase, glutathione

peroxidase , and glutathione reductase and various non-enzymatic compounds (reduced glutathione, iron-binding proteins, antioxidant vitamins, uric acid and so on). It is believed that imbalance between the rates of free radical production and their inactivation by antioxidant defense systems may lead to the development of various severe pathologies including tumors, degenerative, age-associated, and environment-induced diseases , and inflammatory and allergic states. Most of these pathologies were found after the acute or chronic irradiation of an organism.

The main aim of this study was to elucidate safety and clinical efficacy of BN in the treatment of the Chernobyl liquidators in order to combat secondary immunodeficiency and atherosclerosis associated with accidental irradiation, and to diminish degenerative processes in central nervous system.

PATIENTS.

Patients eligible for this study were those with total absorbed dose of irradiation from 0.43 Gy to 2.98 Gy. All patients had measurable or evaluble cardio-vascular, psycho-neural, digestive or degenerative disease , or/and the immune system disorder. Patients suffered from alcoholism, with a poor compliance, mental disorders, and rapidly progressive visceral diseases were ineligible.

STUDY DESIGN.

Eligible patients were randomised to receive either conventional therapy plus placebo (Control groups, 25 patients) or conventional therapy plus BN at appropriate dosage (Experimental groups, 61 patients). The placebo resembled the BN sachet in size, colour,

shape and taste. The study was double-blind with both patients and treating physicians unaware of which study agent was given. The method of randomization was based on a randomised block design, by means of tables of random numbers.

TREATMENT PLAN.

Patients of both groups received conventional therapy being examined by treating physicians daily. In addition, the experimental group of patients received either 3g or 6 g of BN at bedtime daily for 28 days. At the same time, the control group patients received 3g of placebo sweet powder.

STUDY PARAMETERS.

Before entry, the patients were interviewed about occupation with a special stress on the occupational hazards, length of service in Cernobyl, smoking habits, prior medication. Absorbed doses of Cs-137 and Sr-90 (the total dosage of the whole body irradiation) were determined on the basis of measurements made in the early stages after accident and assumption concerning intake. Known disease was documented at trial entry by patients' complains, clinical examination, serum biochemistry, and hematological parameters. Among special analyses, the patients's immunological and free radical status were determined. All blood samples were obtained after at least 10 hours of fasting. Measurements were performed at least two times at baseline and after cessation of the clinical trial. Selected analyses required to follow the underlined disease were repeated weekly.

STATISTICAL METHODS.

Results are median and SEM. Analysis of paired data such as biochemical, hematological, immunological, and free radical measurements before and after trial was

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STATISTICAL METHODS.

Results are median and SEM. Analysis of paired data such as biochemical, hematological, immunological, and free radical measurements before and after trial was

performed using Student's 2 tailed *t* test. Comparisons between two groups studied were made using a Mann-Whitney U test.

ETHICAL CONSIDERATIONS

The protocol complied with the Helsinki Guidelines on human rights and the protocol was reviewed and approved by Ethics Committees of both Radiological Centres. All participants gave written informed consent prior to randomisation.

RESULTS

Eighty-six patients, who satisfied the inclusion criteria were randomised, and there were no subsequently drop-outs from the trial. Of the 86 patients analysed, 61 were treated with conventional therapy plus BN and 25 with conventional therapy and placebo. The two groups were comparable with regard to baseline variables, and the patients did not differ much with regard to total dose of whole body irradiation (Table 1). The total absorbed doses of irradiation varied from 0. 43 to 2.98 Gy. The two groups were well balanced for all on-study characteristics. Patients of the two groups suffered from different cardio-vascular, psycho-neurological, gastro-intestinal, and degenerative diseases (Table 2). BN was well tolerated by all patients, and no side effects were observed. There were no drop-outs from the trial due to patients' intolerability, allergy, or other reasons. Body weight remained unchanged during the study. In both groups marked abnormalities or significant changes were not observed in serum values for hepatic enzymes, bilirubin, total proteins, urea, and creatinine at the beginning and during the treatment. There were no abnormalities in the patients' blood cell count at the beginning and after cessation of the clinical trial.

Blood Biochemistry

There were no significant differences in the blood glucose content (Table 3) as well as in biochemical parameters characterised liver (Tables 4-10) and kidney functions at the beginning and during the clinical study (The levels of creatinine and urea were determined. Data not shown). The mean values of all these parameters were initially in the normal range. BN administration did not affect also initially normal blood cell count and the hemoglobin content in the experimental group patients (Tables 11-13).

Immune Status

The patients' immune status was assessed using various modern approaches such as Coulter Counter for the differential cell count determination. Subpopulations of lymphocytes were measured by flow cytofluorometric method (FACStar plus, Becton Dickinson, USA) using the appropriate monoclonal antibodies preloaded with fluorescein isothiocyonate (Simultest, Becton Dickinson, USA). Data were processed using Software "FACStar plus". The concentrations of IgG, IgA, and IgM were determined by the radial diffusion method. In some cases the concentration of circulating immune complexes were measured using the precipitation method.

Initially, practically all the patients studied (80-92%) possessed the normal levels of CD3+, CD19+ and different classes of immunoglobulins as well as the normal functions of phagocytosing cells. At the same time, the more sensitive immunological parameters such as CD4+, CD8+, and the CD4+/CD8+ ratio were to some extent changed comparing with those of normal subjects, maybe due to irradiation exposure. We did not find any statistically significant changes in the mean values characterised the patients' immunological status, such as lymphocyte subpopulation, phagocytosis and immunoglobulin content (Tables 14-20). However, the mean value of CD4+/CD8+ ratio increased significantly

(1.0 *vs* 1.5; P<0.05) in one of the experimental groups treated with 6g BN. It should be noted also that in some cases (Patients 1, 3, 4, 5, 6, 9, 10, 11, 12, 21, 25, 26, 28 from Kiev group; Patients 6, 7, 9, 10, 15 from Obninsk group) the impaired immunological parameters were found during the preselection period. BN administration significantly improved the initially abnormal lymphocyte subpopulations and immunoglobulin content (See Case Reports). These individual changes were not available for statistical evaluation.

Free Radical Status

A more complicated picture was found when the patients' free radical status was analysed. Practically all patients with a history of exposure to accidental irradiation exhibited an impaired balance between oxygen radical production and detoxification. Thus, the level of lipid peroxidation in plasma, measured by TBA-reactive products was greater than the normal one (47.0 μM/mL plasma *vs* 34.2 μM/mL plasma) and the total antioxidant activity of plasma was significantly lower than that of donors (900 U *vs* 1650 U). However, after a short-term BN administration the amount of TBA-reactive products became lower and the plasma antioxidant activity increased comparing with the initial values (Tables 21 and 24). Both dosages used were effective in the inhibition of lipid peroxidation but only 3 g BN a day improved the plasma antioxidant capacity. Given at the dose 6g a day, BN increased the reduced glutathione level in erythrocytes practically up to the normal level (Table 25). At the same time, BN did not affect glutathione-metabolising enzymes either glutathione peroxidase(Table 26) or glutathione reductase (Table 27). According to data obtained in Ukrainian Radiological Center, BN administration induced the activity of both intracellular antioxidant enzymes superoxide dismutase and catalase (Tables 22 and 23). All the above mentioned parameters of patients' free radical status did not significantly

changed in the control group patients. In general, study of free radical status upon BN therapeutic course showed that BN is capable of eliminating the danger of free radical attack towards biologically active molecules and cellular structures. It, in turns results in non-specific prevention or/and cure of irradiation-induced free radical-mediated pathologies.

Clinical Efficacy

(a) Cardio-vascular system

Most of the irradiated patients who participated in the study suffered from different kind of cardio-vascular diseases (Table 2), among them angina pectoris, atherocoronarosclerosis, ischemic heart disease, essential arterial hypertension, and the combination of the two last pathologies. Their clinical conditions were assessed using conventional diagnostic procedures including the two-hour continous blood pressure recording, electrocardiography (Bioset-6000, USA), echocardiography (SAL 77A, Toshiba, Japan), veloergometry, etc. The data were statistically evaluated using IBM PC supplied with the Quattro Pro, version 5.0 program.

The mean values of both systolic and diastolic blood pressure were found in a normal range at the beginning of the study and did not statistically significantly changed in all groups studied (Data not shown). However, after selection of hypertensive patients (37 subjects), the normotensive effect of BN administration became quite obvious (Table 28). It is seen from this Table that 6g of BN a day decreased the patients' systolic pressure by 22-11 mm Hg and diastolic pressure by 11-6 mm Hg. The daily dosage of 3 g BN decreased systolic pressure by 9 mm Hg and diastolic pressure by 4 mm Hg. There were no changes in blood pressure of the control group patients. In parallel with this positive

therapeutic action, BN improved substantially the insufficiency of hypertrophic left ventricle in hypertensive patients. As it was shown using echocardiography, 6g of BN a day given to patients with cardiac hypertrophy resulted in the normalization of cardiac blood output, myocardium contractility, and the excersion of both dorsal left ventricle wall and interventricular septum (Table 29).

Besides that, the impaired physical capacity of such patients was improved (Table 30) as was shown by physical exertion of patients and the veloergometry method. It was found that before entering the clinical trial, the physical capacity of patients of the different groups did not differ. After therapeutic course with 3 g BN, the threshold physical power (TPP) increased up to 10.8%. The energy-consuming efficacy (ECE) during physical exertion also improved significantly in this group of patients. There were no changes of physical capacity in the control and 6 g BN groups.

(b) Psycho-neurological status

The neurological status study was carried out using conventional diagnostic procedures. To perform psychological examination, the tests and questionaire developed by MMPI (WHO) were used. To confirm diagnosis of neurological disorder, the brain blood flow was measured by the rheoencephalography and ultrasound scanning method (Vazoflo-3, Sonikaid, England), and the brain bioelectrical activity was assessed using an encephalograph (Berg-Fourie Analyzer, Biomedica, Italy). The results of neurological examination showed that 48% of all patients participated in the trial were subjected to vegeto-dystonic syndrome, 34 % to cerebral hypertension, stage II, 9% to cerebral atherosclerosis in combination with hypertension. Practically all patients were complaining

of either constant or intermittent headaches, dizziness, increased irritability, blue mood, disturbance of memory, episodes of blood pressure elevation.

The positive dynamics of general psycho-neurological conditions was registered at the end of clinical study in two experimental groups of patients who were treated with BN. There was no difference between those two groups. During clinical study and after its cessation the patients' psycho-neurological status improved significantly because more than 50% of patients given 3 or 6 g BN slept better; the frequency of headache and dizziness attacks decreased; fatigue, irritability and dystonic syndrome decreased. Treating physicians explained these facts in terms of improvement of cerebral metabolism.

CONCLUSIONS

1. BN administration to the Chernobyl disaster liquidators was completely safe and was not associated with any adverse effects as apparent from vital signs and a variety of clinico-chemical parameters for liver and kidney functions and blood cell count. The consumption of comparatively large dosage of BN a day during 1 month did not affect the patients' carbohydrate metabolism.

2. BN diminished significantly oxidative stress, which is a charactestic feature for people subjected to irradiation. BN administration decreased the intensity of lipid peroxidation and increased the total antioxidant capacity of plasma, the reduced glutathione content, and activities of main antioxidant enzymes in blood cells. This may be relevant to the prevention, amelioration, and cure of the radiation-induced free radical-mediated pathologies.

3. BN may be regarded now as a hypotensive agent capable of decreasing the elevated blood pressure in patients with a primary essential hypertension. It also improved the insufficient functions of hypertrophic left heart ventricle in such patients.

4. BN increased the patients' impaired physical capacity by optimization of energy-consuming processes.

5. The beneficial effect of BN on the psycho-neurological status of irradiated patients was observed. It decreased headache and dizziness, improved sleep and mood, ameliorated dystonic syndrome, vegetative neurosis and irritation.

Study supervisor

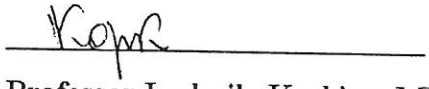

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Table 1. Baseline variables for the three study groups

Variable	Group		
	Control (n = 25)	3 g BN (n = 16)	6 g BN (n = 45)
Age (years)	43 (32÷54)	45 (34÷59)	44 (32÷55)
Sex (F/M)	2F/19M	0F/16M	5F/44M
Number of smokers	11	7	23
Dosage of irradiation (Gy)	0.5÷2.44	0.56÷2.67	0.7÷2.98
Hemoglobin content (g/L)	148.5 ± 8	153 ± 5	152 ± 8.5
Glycemia (mmol/L)	5.12 ± 0.43	5.13 ± 0.41	5.76 ± 1.35

Table 2. On study patients' characteristics

	Group		
	Control	3 g BN	6 g BN
Age (years)	43 (32÷54)	45 (34÷59)	44 (32÷55)
Ischemic heart disease	23%	21%	20%
Arterial hypertension	32%	30%	37%
Atherosclerosis + arterial hypertension	8%	10%	8.5%
Neurovascular dystonia	46%	48%	48%
Encephalopathy	78%	82%	80%
Chronic gastritis, cholecystitis, duodenitis, and colitis	4%	4%	5%
Others	9%	13%	10%

Table 3
Glucose content (mM/L)

Patients from Obninsk	
Group A (BN, 6g a day), 30 patients	Group B (Control), 10 patients
5.84±2.04 (First visit)	4.79±0.27 (First visit)
4.71±0.55 (Second visit)	4.77±0.24 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
5.13±0.41 (First visit)	5.44±0.59 (First visit)
5.49±0.45 (Second visit)	5.29±0.37 (Second visit)
Group B (BN, 6 g a day), 15 patients	
5.68±0.66 (First visit)	
5.57±0.66 (Second visit)	

Table 4
Total bilirubin (mM/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control) 10 patients
15.6±3.9 (First visit)	14.4±3.4 (First visit)
13.2±3.5 (Second visit)	11.1±3.0 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
12.0± 2.2 (First visit)	14.4± 5.8 (First visit)
11.7±4.1 (Second visit)	14.7±4.1 (Second visit)
Group B (BN, 6 g a day), 15 patients	
14.9±4.7 (First visit)	
14.2±7.5 (Second visit)	

Table 5
Total protein content (g/L)

Patients from Obninsk	
Group A (BN, 6 g a day) 30 patients	Group B (Control), 10 patients
67.7±8.0 (First visit)	71.1±5.7 (First visit)
66.1±7.6 (Second visit)	71.1±4.9 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
76.1± 5.2 (First visit)	80.4±6.8 (First visit)
77.7±5.9 (Second visit)	81.0±5.9 (Second visit)
Group B (BN, 6 g a day), 15 patients	
83.1±10.6 (First visit)	
79.5±3.4 (Second visit)	

Table 6
ALT content (U/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
25.0±10.7 (First visit)	26.1±11.5 (First visit)
25.4±11.3 (Second visit)	30.3±15.9 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control) 15 patients
29.7±15.0 (First visit)	23.3±15.3 (First visit)
28.5±13.6 (Second visit)	23.7±9.0 (Second visit)
Group B (BN, 6 g a day), 15 patients	
24.1±7.7 (First visit)	
27.0±10.6 (Second visit)	

Table 7
AST content (U/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
20.2±7.2 (First visit)	21.9±9.3 (First visit)
19.9±5.6 (Second visit)	20.3±4.0 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
28.3±9.4 (First visit)	24.9±8.1 (First visit)
25.5±6.4 (Second visit)	27.8±7.5 (Second visit)
Group B (BN, 6 g a day), 15 patients	
26.1±12.0 (First visit)	
28.5±9.7 (Second visit)	

Table 8
Cholesterol content (mM/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
5.81±1.17 (First visit)	5.32±1.04 (First visit)
5.78±1.14 (Second visit)	5.28±1.06 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control) 15 patients
5.94± 1.22 (First visit)	6.38±0.86 (First visit)
5.84±0.93 (Second visit)	6.29±0.95 (Second visit)
Group B (BN, 6 g a day), 15 patients	
6.11±1.52 (First visit)	
5.84± 1.50 (Second visit)	

Table 9

β-Lipoprotein content

Patients from Obninsk			
Group A (BN, 6 g a day), 30 patients		Group B (Control), 10 patients	
59.3±14.1	(First visit)	59.0±13.8	(First visit)
58.4±14.3	(Second visit)	52.6±12.5	(Second visit)

Table 10

Triglyceride content

Patients from Obninsk			
Group A (BN, 6 g a day), 30 patients		Group B (Control), 10 patients	
1.85±0.60	(First visit)	1.92±0.71	(First visit)
2.10±0.74	(Second visit)	1.92±0.87	(Second visit)

Table 11

Hemoglobin content (g/L)

Patients from Obninsk			
Group A (BN, 6 g a day), 30 patients		Group B (Control), 10 patients	
143±8	(First visit)	140±9	(First visit)
141±7	(Second visit)	138±9	(Second visit)
Patients from Kiev			
Group A (BN, 3 g a day), 16 patients		Group C (Control) 15 patients	
153±5	(First visit)	157±7	(First visit)
159±14	(Second visit)	153±5	(Second visit)
Group B (BN, 6 g a day), 15 patients			
160±9	(First visit)		
159± 9	(Second visit)		

Table 12
RBC content ($\times 10^{12}$/L)

Patients from Obninsk	
Group A (BN. 6 g a day), 30 patients	Group B (Control), 10 patients
4.59±0.34 (First visit)	4.50±0.26 (First visit)
4.61±0.26 (Second visit)	4.52±0.23 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
4.75±0.37 (First visit)	5.01±0.38 (First visit)
4.98±0.43 (Second visit)	5.07±0.93 (Second visit)
Group B (BN, 6 g a day), 15 patients	
5.12±0.36 (First visit)	
4.99±0.35 (Second visit)	

Table 13 WBC content (10^9/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
6.47±1.72 (First visit)	6.20±1.39 (First visit)
6.69±1.49 (Second visit)	6.69±1.49 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
7.11±3.55 (First visit)	7.39±1.63 (First visit)
6.85±1.80 (Second visit)	6.59±1.15 (Second visit)
Group B (BN, 6 g a day) 15 patients	
6.24±1.41 (First visit)	
6.21±1.49 (Second visit)	

Table 14 CD4+

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
49.1±8.5 (First visit)	43.2±4.5 (First visit)
48.1±7.3 (Second visit)	48.1±5.7 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
40.6±8.6 (First visit)	39.5±5.4 (First visit)
38.3±7.7 (Second visit)	39.0±5.4 (Second visit)
Group B (BN, 6 g a day), 15 patients	
34.0±6.9 (First visit)	
43.3±6.6 (Second visit)	

Table 15 CD8+

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
26.7±6.8 (First visit)	27.1±8.0 (First visit)
26.8±6.3 (Second visit)	26.7±6.8 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
27.4±7.6 (First visit)	31.0±3.9 (First visit)
31.8±8.2 (Second visit)	30.0±6.2 (Second visit)
Group B (BN, 6 g a day), 15 patients	
33.7±6.6 (First visit)	
30.6±6.6 (Second visit)	

Table 16 IgG (g/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
13.2±1.6 (First visit)	12.4±2.1 (First visit)
12.9±1.6 (Second visit)	12.4±1.2 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
8.8±3.0 (First visit)	10.9 ± 1.4 (First visit)
9.8±1.9 (Second visit)	7.9±1.9 (Second visit)
Group B (BN, 6 g a day), 15 patients	
10.7±1.9 (First visit)	
11.3±1.7 (Second visit)	

Table 17 IgA (g/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
1.95±0.38 (First visit)	1.90±0.24 (First visit)
2.04±0.38 (Second visit)	2.08±0.25 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
1.86±0.78 (First visit)	2.01±0.58 (First visit)
1.91±0.45 (Second visit)	1.74±0.52 (Second visit)
Group B (BN, 6 g a day), 15 patients	
2.11±0.33 (First visit)	
2.18±0.56 (Second visit)	

Table 18 IgM (g/L)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
1.54±0.31 (First visit)	1.21±0.24 (First visit)
1.51±0.33 (Second visit)	1.25±0.31 (Second visit)
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
0.91±0.56 (First visit)	1.03±0.24 (First visit)
0.90±0.45 (Second visit)	1.13±0.47 (Second visit)
Group B (BN, 6 g a day), 15 patients	
0.96±0.25 (First visit)	
0.83±0.43 (Second visit)	

Table 19
Phagocytozing number (PN)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
58.7±3.1 (First visit)	59.7±7.0 (First visit)
60.3±5.2 (Second visit)	60.8±6.2 (Second visit)

Table 20
Phagocytozing index (PI)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	Group B (Control), 10 patients
4.70±0.56 (First visit)	5.08±0.72 (First visit)
5.25±0.98 (Second visit)	5.27±1.00 (Second visit)

Table 21
MDA content (μM/mL plasma)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	
44.5±5.2 *) (First visit)	
36.2±4.8 *) (Second visit)	
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
48.2±6.3*)**) (First visit)	45.8±10.1 (First visit)
38.6±4.1*) (Second visit)	45.6±5.6 (Second visit)
Group B (BN, 6 g a day), 15 patients	
49.4±6.0*)**) (First visit)	
38.5±4.1*) (Second visit)	

*) Value before vs. after BN administration, $P_1<0.05$.
**) Experimental value vs. control, $P_2>0.05$

Table 22
SOD activity (mg/g Hb)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	
1.81±0.23*) (First visit)	
1.77±0.16*) (Second visit)	
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
3.10±0.43*)**) (First visit)	3.18±0.34 (First visit)
3.95±0.43*) (Second visit)	3.22±0.29 (Second visit)
Group B (BN, 6 g a day), 15 patients	
3.50±0.33*)**) (First visit)	
4.88±0.23*) (Second visit)	

$P_1'>0.05$; $P_1''<0.05$; $P_1'''<0.01$; $P_2'>0.05$; $P_2''>0.05$

Table 23
Catalase activity (mg/gHb)

Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
1060±160*) (First visit)	1600±100 (First visit)
1300±140*) (Second visit)	1470±160 (Second visit)
Group B (BN, 6 g a day), 15 patients	
1100±120*) (First visit)	
1350±150*) (Second visit)	

P_1'<0.05, P_1''<0.05

Table 24
Plasma antioxidant activity (U)

Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
790±40*) (First visit)	1200± 160 (First visit)
1430±110*) (Second visit)	1250±200 (Second visit)
Group B (BN, 6 g a day), 15 patients	
800±120*) (First visit)	
940±100*) (Second visit)	

P_1'<0.01, P_1''<0.05

Table 25
GSH content (μM/gHb)

Patients from Obninsk	
Group A (BN, 6 g a day), 30 patients	
3.43±0.92*) (First visit)	
4.88±0.81*) (Second visit)	
Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
4.90±0.62*)**) (First visit)	4.41±0.61**) (First visit)
3.20±0.33*) (Second visit)	3.26±0.41 (Second visit)
Group B (BN, 6 g a day), 15 patients	
3.98±0.41*) (First visit)	
4.58±0.51*) (Second visit)	

$P_1' < 0.05$, $P_1'' > 0.05$, $P_2 > 0.05$

Table 26
Glutathione peroxidase activity (μM/L)

Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
190±20 (First visit)	194±10 (First visit)
200±15 (Second visit)	190±15 (Second visit)
Group B (BN, 6 g a day), 15 patients	
230±15 (First visit)	
210±20 (Second visit)	

Table 27
Glutathione reductase activity (μM/L)

Patients from Kiev	
Group A (BN, 3 g a day), 16 patients	Group C (Control), 15 patients
825±50 (First visit)	770±60 (First visit)
830±50 (Second visit)	780±90 (Second visit)
Group B (BN, 6 g a day), 15 patients	
880±90 (First visit)	
1000±150 (Second visit)	

Table 28
Blood pressure

Patients from Obninsk			
Group A (BN, 6 g a day), 16 patients		Group B (Control), 10 patients	
Systolic	Diastolic	Systolic	Diastolic
149±10*) (First visit)	94±6*) (First visit)	130±5 (First visit)	85±5 (First visit)
127±6*) (Second visit)	83±4*) (Second visit)	128±4 (Second visit)	82±3 (Second visit)
Patients from Kiev			
Group A (BN, 3 g a day), 9 patients		Group C (Control), 15 patients	
Systolic	Diastolic	Cyctolic	Diastolic
152±2*)(First visit)	96±1*) (First visit)	132± 5 (First visit)	82±2 (First visit)
143±2*) (Second visit)	92±1*) (Second visit)	130±4 (Second visit)	83±2 (Second visit)
Group B (BN, 6 g a day), 12 patients			
Systolic	Diastolic		
148±4*)(First visit)	91±3*) (First visit)		
137± 4*) (Second visit)	85±2*) (Second visit)		

P_1'<0.05, P_1''<0.01, P_1'''<0.01

Table 29. Cardiac functions in patients with the left ventricle hypertrophy

Parameter	3 g BN group		6 g BN group		Control	
	Basal	4 weeks	Basal	4 weeks	Basal	4 weeks
Volume of cardiac output (ml/min)	79.0±2.7	79.8±2.4	81.3±2.1	85.4±2.5 p<0.05	85.7±3.0	84.0±2.8
Rate of the diastolic myocardium contraction (mm/sec)	72.2±2.8	73.1±2.1	87.3±3.2	78.2±2.9 p<0.05	70.2±2.4	70.4±2.5
Excersion of interventricular septum (mm)	7.8±0.4	7.1±0.3	8.3±0.4	7.2±0.5 p<0.05	7.5±0.6	7.1±0.4
Excersion of dorsal left ventricle wall (mm)	10.0±0.3	10.1±0.1	12.2±0.3	10.4±0.2 p<0.05	10.4±0.5	10.4±0.4

Table 30. Physical capacity of patients

Parameter	3 g BN group		6 g BN group		Control	
	Basal	4 weeks	Basal	4 weeks	Basal	4 weeks
Threshold physical power (Wt)	108.3±5.4	120.0±5.6 $p<0.05$	119.2±5.6	123.1±5.8	118.3±6.5	118.3±6.5
Energy-consuming efficacy without physical overload (arb. units)	111.1±8.1	89.7±7.9 $p<0.05$	107.9±8.1	112.8±7.6	96.7±8.2	96.9±8.4
Energy-consuming efficacy with physical overload (arb. units)	218±22	188±21 $p<0.05$	254±21	241±22	274±19	241±17