

Ministry of Health and Social
Development of the
Russian Federation

Transfer Factors Use in
Immunorehabilitation After
Infectious-Inflammatory and
Somatic Diseases

METHODOLOGICAL LETTER

Moscow, 2004

MINISTRY OF HEALTH AND SOCIAL
DEVELOPMENT OF THE
RUSSIAN FEDERATION

“APPROVED”

Director of Medical Service and
the Department of Treatment Development
for Health Recovery Resorts (Kurortology)

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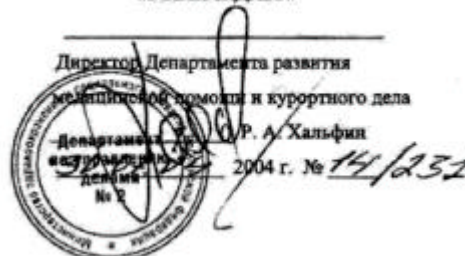
R A Khalfin,
30.07.04 No. 14/231

TRANSFER FACTORS USE IN
IMMUNOREHABILITATION AFTER
INFECTIOUS-INFLAMMATORY
AND SOMATIC DISEASES

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«УТВЕРЖДАЮ»



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Published by:
Center of MicroNutrientology
Moscow, Russian Federation

Printed in the United States of America.

This communication presents the results of clinical trials, which were designed to study the effectiveness of a complex colostrum derived product, Transfer Factor™ (and Transfer Factor Plus™), in various pathological conditions and to study the influence of cellular mediators, which are incorporated in Transfer Factor, on different components of the immune system. The authors give recommendations concerning the use of Transfer Factor products in medical practice.

This methodology letter was considered and approved at the Central Coordination meeting of the Methodological Council of Altay State Medical University (protocol No 4, 05.11.2033) and sent to the Ministry of Health and Social Development of the Russian Federation for their consideration.

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1. Preface

Advances of civilization, scientific and technical progress and achievements in medicine have not helped to reduce the incidence of infectious and non-infectious diseases among the populations of the planet. On the contrary, the number of oncological, cardiovascular, respiratory and endocrine diseases and neuropsychiatric disorders is growing.

A new group of so-called emerging infections, including AIDS, parenteral types of hepatitis and others have appeared. The Earth's population experienced a decrease in general resistance due to globally unfavorable social (malnutrition), ecological (the atmosphere and the environment pollution with many from modern technology) and medical (unjustified use of some medicines, narcotics, alcohol, stress and so on) factors that are some of the causes of the existing situation. All of these factors are pernicious to the immune system and can cause immunodeficiency.

The use of immune modulators is one of the principal means in maintaining normal immune system function and in restoring immunity in immunodeficient conditions. Immune modulators both natural and synthetic substances are capable of stimulating or suppressing the immune system.

A multitude of immune modulators are used in medical practice but their effectiveness and the other properties defining their safety, simplicity in use and economy factors differ greatly (A.A. Vorobiev, RAMS Bulletin, #4, 2002). Natural, endogenous immune modulators, which contain basic substances that take part in the processes of immune regulation, are the most acceptable and adequate for humans. Being composed of natural peptides obtained from cow colostrum Transfer Factor™ is considered to be one such immune modulators. The main function of these peptides in the body is to provide immune protection against microbes (bacteria, viruses, fungi, protozoa), cancerous cells, and other antigens capable of disturbing vital processes in the body.

Transfer Factors stimulate the cellular arm of the immune system (killer lymphocytes in particular), activate immunocytokine synthesis, and regulate immune functions. Transfer Factor is superior to other, even well known immune modulators being extremely effective in boosting the immune system. It possesses a broad spectrum of action, is safe, is used orally as gelatinous capsules, has no contraindications, causes no adverse reactions and is effective both in adults and children.

Transfer Factor has been successfully used for many years for the treatment and prevention of bacterial, viral, fungal infections, parasitic disease, malignant tumors, autoimmune conditions, neurasthenic, allergic and endocrine disorders, primary and secondary immunodeficiencies and in diseases accompanied by disturbances in immune functions.

Transfer Factor™ and Transfer Factor Plus® products have been extensively studied in Russian clinics and research institutions. This helped to generalize clinical results into the form of methodological recommendations. This methodological letter is meant to acquaint physicians, medical students, clinical residents and post graduates with current information, concerning the mechanisms of the immune system response to exogenous factors of viral and bacterial origin, with the properties of Transfer Factor products and the results of the studies aimed at the evaluation of their effectiveness in various pathological conditions.

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2. Current Concepts of the Development of Immune Response Mechanisms and the Restoration Principles of Impaired Functions of Immunocompetent Cells

The last decades of the 20th century and the beginning of the 21st century are characterized by a high rate of infectious diseases connected with proliferation of pathogenic microorganisms and an increased aggressiveness of opportunistic microflora.

The significance of the problem of infectious diseases prevention has become especially pressing due both to the emergence of formerly unknown diseases (AIDS) and the absence of the effective prophylactic treatments for a number of well known infections (acute respiratory diseases, acute intestinal infections, etc).

The high rate of viral and bacterial infections is caused not only by resistance developed by microorganisms but also by disorders in the host's protective mechanisms resulting from numerous external and internal risk factors, and from congenital and acquired immunodeficiency.

Despite noticeable advances in the field of specific prophylaxis and antibacterial therapy of infectious diseases, the problem is still very pressing due to the acquired resistance by pathogenic microorganisms to modern methods of treatment. The situation appears to be an everlasting struggle between pathogenic microorganisms and humanity in the struggle for survival. In this situation the only alternative to vaccination or antibacterial therapy may be the use of immunomodulators that improve specific and nonspecific immunity against infections and regulation of immune system function. Immunomodulators may prove to be very valuable in strengthening specific immunoprophylaxis during emergency stimulations when the body's defensive mechanisms meet the challenge of a virulent infection, in confronting an unknown pathogenic organism, in cases of an increased risk of infection, or conventional treatment failures.

Antigen immunogenicity and recognition play an important role in defining the character of interrelations between a foreign agent and the host and the formation of adequate specific immunity (35, 48). Phagocytosis of microorganisms followed by intracellular digestion is the initial phase of an immune reaction. Polymorphonuclear neutrophils and macrophages are the main phagocytic cells. A cascade of enzyme reactions promote activation of the humoral immunity linked non-specific factors (complement components), thus increasing capillary permeability, enhancing Polymorphonuclear leukocytes chemotaxis and resulting in the ingestion of microorganisms by phagocytes. Numerous intracellular oxygen dependent and oxygen independent bactericidal mechanisms are then employed. The inflow of Polymorphonuclear leukocytes and increased vascular permeability lead to a powerful acute inflammatory antimicrobial reaction.

Certain specific antibodies destroy microorganisms that either fail to trigger an alternative pathway of complement activation or prevent phagocytic cell activation. An antibody forms a complex with an antigen and activates complement in a classical manner followed by enhanced Phagocytosis.

Antibodies are formed by plasma cells, B-lymphocytes being their precursors. Each B-lymphocyte is programmed to synthesize certain specific antibodies consisting of IgA, IgM, IgG, IgE or IgD.

Another lymphocyte population, namely T-lymphocytes, controls other types of disease agents including intracellular infections. Like B-lymphocytes, each T-lymphocyte is provided with a specific receptor, which recognizes an antigen. Later T0-cells are differentiated into subpopulations forming T-helpers (Th), which participate in the formation of cytotoxic T-

lymphocytes and T-suppressors (Ts), which monitor the strength of immune response and natural killer (NK) cell response.

The two-stage system of specific immune response development which has been confirmed both experimentally and clinically, is a vivid illustration of an antigen's highly immunogenic influence (49). According to this concept it is the directive activity of cellular mediators (cytokine) that causes macrophage activation, Phagocytosis of microbes (viruses) and presentation of the most immunogenic antigens to T-lymphocytes with ensuing differentiation. It is established that during the first stage of immune response a macrophage is activated both by its own cytokines (IL-1) and by cytokines (macrophage activating factor, IL-2 & 4, INF-a, INF-g) produced by the Th0 lymphocytes. This complex of cytokines is understood to induce activity of the 2nd class of antigens of the Major Histocompatibility Complex (MHC), which are on the membranes of antigen presenting cells (49, 51, 56). Macrophages and other antigen presenting cells present the antigens to T0-lymphocytes to trigger the specific cellular response phase of immune response.

It should be pointed out that both production and activation of cellular reaction mediators (cytokines) under physiological conditions occur simultaneously with the cytokines functioning as a unified harmonious system. An impact on any one component of the immune system inevitably affects the function of its other components (50). This forms the basis of the modern theory of the immune system network regulation (24, 50), which postulates that each single element of immune cytokine regulation is functionally related to many other elements.

Thus, the entire cytokine system is a network structure undergoing constant interaction among its different components and this is why an imbalance of the cytokine network function lies at the basis of pathological manifestations in many diseases (41). Both the type of immune response and the processes of cellular proliferation and differentiation in the hemopoietic and immune systems depend on cell mediator balance.

Previously, R.M. Khaitov and B.V. Pinegin (49) presented a scheme describing the staged development of a specific immune response to a highly immunogenic antigen of bacterial or viral origin. According to the scheme, infectious antigens first activate non-specific preimmune resistance mechanisms including:

- Factors of natural resistance that are more active during the first 4 hours;
- Factors of an early inducible response that last for 96 hours.

In light of modern findings the interrelations and the roles of populations and subpopulations of lymphocytes and cytokines, the mechanisms of interaction of all component factors of non-specific monocytic-macrophagal origin, and the importance of the activity of class 1 and class 2 antigens of the MHC for the development of a specific phase of the immune response, are defined and stressed at all stages of development of immune response.

The effect of antigens with low immunogenic response differs strongly from that of antigens with high immunogenic response. Low responders are not capable of reacting with antigen presenting cells, of causing activation of the immune system macrophagal response with the production of the first phase cytokines, or of increasing the number of the class 2 antigens of the MHC (1, 2). In chronic infectious-inflammatory diseases caused by opportunistic flora, the monocytic-macrophagal phase is not activated and the presentation of the complex (antigen plus class 2 MHC determinant) to Th0-lymphocytes followed by the development of the specific phase of the immune response does not take place.

The formation of an adequate and stable immunity resulting from vaccinations of children depends not only on the immunogenic properties of the antigens of the immune response, but

on the strength as well as the decisiveness of the immune response. Weak immune or atopic type immune responses do not mount a strong initial and collective resistance to infection.

The preferential production and activation of certain cytokines may be a marker of a given pathological condition. Thus, children suffering from upper respiratory tract inflammatory diseases with frequent exacerbations that respond poorly to traditional therapy, exhibit increased production of proinflammatory cytokines (47). Long term immune function under conditions of chronic recurrent infection probably leads to a shift in cytokine balance to an altered quantitative and qualitative scale accompanied with a constant stimulus for their expression, thus supporting the inflammatory process. In this situation immunomodulating therapy may contribute to renewed response and initially to the production of proinflammatory cytokines activating an otherwise quiescent process against the infection. A well known approach to the treatment of persistent dormant infections is based on this principle. It is aimed at their provocation followed by effective complex treatment. There are convincing clinical and experimental data on the use of certain stimulating immunomodulators being used to activate the monocytic-macrophagal link of the immune system (15, 3). Sodium nucleinate myelopid, likopid, polyoxidony, echinacea and others are among such immunomodulators (14, 17, 23).

The main treatment for non-specific immunotherapy activation is the use of interferon (IFN) products (amyxin, cycloferon, neovir), macrophages, B- and T-lymphocytes as stimulators (thymus products, pirogenal, prodigiosan, etc), natural and recombinant IFN with antiviral and immunomodulating effects as well as interleukins and other cytokines. In some patients IFN therapy produces side effects and induces autoimmune processes. Thus, even such popular agents as IFN can not be regarded as a panacea and their effectiveness in certain viral infections does not exceed 30-50%.

Cytokines are known to regulate the function of antigen presenting cells, thus markedly shortening the period of specific antibody production and enhancing the presentation of antigens to immunocompetent cells.

Chronic inflammation is a condition of unstable equilibrium between clinically mild protracted inflammatory processes and the response of immunocompetent cells. Disturbance of this equilibrium may be induced by an additional infection or by immunosuppressive agents, which suppress the effect or functions of the immune system. Each exacerbation of a chronic inflammatory process activates the immune system and restores equilibrium at another, lower level of defense. Immunocorrecting therapy should be carried out during remission of these chronic infectious-inflammatory diseases. It may be a three-stage regimen:

1st period: intensive immunostimulation (20-30 days)

2nd period: maintenance therapy

3rd period: immunorehabilitation

Immunorehabilitation measures are a central issue of current human biology. At this stage of the regime natural immunomodulators such as photochemical agents, adaptogens, transfer factors, restorative health resorts and other means should be used more extensively.

3. Colostrum Derived Transfer Factors – A New Generation of Immunomodulating Agents

The discovery of transfer factors by H.S. Lawrence in 1949 marked the beginning of a new era in the development of immunology (32, 33, 54). He established that immunity can be transferred from one person to another by injecting a leukocyte extract containing molecules named transfer factors. The superb properties of these immunoactive signal molecules called transfer factors are capable of revolutionizing medicine.

According to Kirkpatrick, *et al* (46) transfer factors are peptides consisting of 44 amino acids. Unlike antibodies, which have large molecular masses, transfer factor molecules are only a small fraction of antibody size and have molecular weights of less than 10,000 daltons. According to some authors the boundaries are between 3,500 to 5,000 daltons.

It was later found that transfer factors are not species specific but possess a versatile effectiveness irrespective of the biological species of donor or recipient. Therefore, they may be sourced from different mammals, i.e. they can transfer immunity to people even if they are derived from a different mammal species. According to literature data transfer factors exert multitudinous impacts on the immune system, regulating functions of T-suppressors, T-killers and macrophages (31).

Transfer Factor™ (TF) (produced by 4Life Research, USA) is a hypoallergenic product, free of casein, lactoglobulins and other large proteins, but it does contain intact cytokine fractions identical to leukocytic cytokines. Academician A.A. Vorobiev of the Russian Academy of Medical Sciences points out that unlike other immunomodulators Transfer Factor has a wide spectrum of activity, is safe, is administered orally, has no contraindications or side effects, and is effective both in adults and children.

Being versatile immunocorrectors transfer factors induces, moderates and/or normalizes immune response. Depending on the type of disturbance it either stimulates weak immunity, or normalizes or enhances protracted immune reactions, thus preventing the onset of pathological processes. These effects are due to the fact that TF has three main fractions with each named according to its main effect on the immune system: inducer, antigen specific and suppressor transfer factors. Inducers provide general readiness of the immune system to ward off aggressors. Antigen specific transfer factors are a set of certain antigens and cytokines which help the immune system to recognize many microorganisms and antigens in advance. Suppressors prevent the immune system from concentrating all its strength on a defeated infection while ignoring other threats. Suppressors also regulate the immune response intensity, thus preventing autoimmune reactions. Cytokines, a part of the composition of TF, regulate suppressor cells functions, help maintain adequate immune reaction and the degree of process activation, i.e. body reactions may become predictable and manageable.

The antigen presenting TF components were found to shorten the period prior to antibody production by augmenting the process of antigen presentation to immunocompetent cells.

As a rule, persistence of chronic infection is known to be due to inadequate phagocytic and digestive functions of macrophages; this protracts the period of foreign antigens presentation to T-lymphocytes, and ensuring antibodies production.

Transfer Factor' variety mechanisms and actions, their natural origin and lack of contraindications broaden the sphere of their application. The antigen specific components of TF influence the activity of macrophages and cytotoxic T-lymphocytes, thus helping the immune system to recognize certain microorganisms and antigens. And, because of the stages of antigen recognition and presentation to antibody producing cells are skipped; it also

markedly enhances the production of specific antibodies by bringing about antibody synthesis with a ready “matrix” of an antigen specific factor.

A very important aspect of the effects of transfer factors is the non-specific activation of macrophagal reactions that contribute to complete Phagocytosis, recognition of any antigens by macrophages, and their presentation to other immunocompetent cells. A similar process is routinely accomplished by macrophages located in Peyer patches in the intestines. In this way a stable level of natural defensive antibodies and the rate of the production of specific antibodies against certain pathogenic microorganisms entering the body via the gastrointestinal tract are regulated.

Nature has devised the most effective and prompt means of protecting infants by transmitting transfer factors from mother to child. During the first hours and days of life information mediators and ready immunoglobulin antibodies entering the body of a newborn via colostrum providing protection not only as a first aid measure upon the encounter of infectious pathogens, but also to “teach” intestinal macrophages and Peyer patch lymphocytes to quickly recognize foreign antigens and trigger protective immune mechanisms.

Scientific interest in transfer factors is accented by the fact that since the time of their discovery more than 40 million US dollars have been spent on their research, more than 3000 scientific papers have been published and eleven international conferences have been held. Despite these facts, the study of structural aspects and the mechanisms of transfer factors effect are still challenging problems for involved scientists (46).

18 defense factors participate to a certain degree in the development of almost every pathological condition. Effective treatment of many infectious, autoimmune and allergic diseases depends on timely use of immunocorrecting drugs. The way a particular immune system responds to detrimental factors and the environment in which a pathological process arises and develops are of great importance. It should be pointed out that since the discovery of transfer factors more than 50 years ago they have become one of the most effective means to strengthening body resistance to various detrimental factors. Their demonstrated immunocorrecting effects in many infectious and somatic diseases have been studied and reported by scientists of different countries.

Transfer factors’ wide spectrum of clinical effects, which were reported at the 11th International symposium (dedicated to transfer factors), encouraged doctors to recommend them to patients of different ages from infants to elderly people being treated in intensive care units. The effectiveness of oral use of transfer factors preparations was also reported.

Due to its great effectiveness TF can be used in combination with other immunomodulators and adaptogens. The use of TF in conjunction with such adaptogens as immunal, tactivin, thymogen, myelopid and others will help to direct their immunomodulating effect along the paths of cytokines and antibody production.

Comparative scientific data obtained from laboratory investigations confirm the stimulating effect on Natural Killer (NK) cells by TF and Transfer Factor Plus®. It has been established that TF is significantly more active than other well know immunomodulators, since TF increased NK activity by 103% and adaptogens fortified TF PLUS by 248% (32, 46).

In-vitro studies carried out by M.V. Kisielevsky and E.O. Khalturina (28) at Russian Cancer Research Center demonstrate mononuclear blood cells from health donors. The greatest effect was recorded 48 hours following mononuclear cell incubation with the products at different concentrations. The level of effective concentrations ranged from 0.1 to 0.0001 mg/ml. These products, which contain mixtures of transfer factors derived from two sources, colostrum and egg yolk, were most effective in proportions 70:30 and 50:50 (bovine:egg). Incubation of these products with mononuclear cell resulted in an average

increase of mononuclear cell cytotoxicity from a low of 18% to 80-99% with and some samples exceeding the cytotoxic stimulating effects of interleukin-2.

Transfer Factor™, a product of 4Life Research, is a proprietary concentrate of transfer factors (Transfer Factor XF™) derived from bovine colostrum by means of an exclusive and patented process. Pharmaceutical form: gelatin capsules, containing Transfer Factor powder (bovine colostrum concentrate) and maltodextrin.

Transfer Factor Plus® is a proprietary product of 4Life Research containing:

- Transfer Factor XF powder (bovine colostrum concentrate)
- Zinc monomethoinine 20% (3.3 mg of zinc)
- Proprietary Cordyvents' mixture
- Inositol hexaphosphate
- Soy beans extract (phytosterols)
- *Cordyceps sinensis*, powder
- Baker's yeast (D-b-glucan) extract
- Lemon, peel powder
- *Agaricus blazeii* Mushroom extract
- Aloe gel powder (*Aloe vera* leaf)
- Oats extract, *avena sativa* (b-glucan)
- Olive tree (*Olea europaea*) leaf powder extract
- Maitake Mushroom (*Grifolea frondsa*) powder extract
- Shitake Mushroom (*Lentinus edodes*) powder extract.

4. The Use of Transfer Factors in Various Diseases

With the diversity of exiting immunomodulators capable of producing either stimulating or suppressing effect on the immune system, we chose to scientifically investigate the use of transfer factor products in pathological conditions necessitating immunocorrection.

Studies demonstrating the clinical and immunological effectiveness of Transfer Factor™ and Transfer Factor Plus® in the treatment of patients with HIV infection, hepatitis B and C, herpes, urogenital chlamydiosis, severe bacterial infections (osteomyelitis), helminthic invasions (opisthorchiasis), as well as malignant tumors (gastric cancer), dermatoses (psoriasis, atopic dermatitis) and duodenal ulcer were carried out in different clinics of Russian Federation from 2000 through 2003.

The results of the clinical studies, included in this paper, helped to evaluate the effectiveness and safety, the duration of treatments, the doses of Transfer Factor products, and prospects of their use not only in the above mentioned diseases, but in the complex treatment of various pathological conditions.

The Effectiveness of TF Use in Viral Hepatitis

Destabilized immune mechanisms play a leading role in the pathogenesis of parenteral hepatitis (viral hepatitis B and C) as well as in the course and outcomes of the diseases (42, 43). Despite considerable experience in viral hepatitis treatment, including chronic ones, a number of issues concerning an optimal regimen are still being discussed with doses and the treatment with interferons (INF) as the current drugs of choice. The fact that treatment with INF of one patient with the chronic form of hepatitis C costs \$10,000-\$15,000 prompts the necessity of solving this issue. In addition, this antiviral therapy prescription has a list of other indications, but interferons are sometimes poorly tolerated by patients and the host produces antibodies against recombinant interferons. For these reasons the search for agents with proven therapeutic effect in the patients with viral hepatitis is quite justified.

The first results obtained from adult patients receiving TF along with the conventional therapy attests to a high effectiveness of cellular cytokines use in this kind of pathology (9). Along with the normalization of biochemical values and the decrease of viral load (62% in most cases), all patients registered a marked improvement of the general state, were more efficient and did not experience excessive fatigue, and there was no discomfort in the right hypochondrium. Further studies with the patients with acute and chronic forms of viral hepatitis B and C, wherein patients were followed up for 6 months after the treatment, were carried out by the same authors (19, 21). Fifty (50) patients with chronic viral hepatitis B and C and 15 patients with acute viral hepatitis B received TF, one capsule 3 times daily for 14 days. The resulting data were comparable to those obtained in patients receiving conventional treatment with interferons.

Twenty four (24) patients with acute hepatitis B and 34 patients with chronic hepatitis C (CVHC) received TF PLUS, 1 capsule 3 times daily for 14 days. The control group, 15 CVHC patients, received 3,000,000 IU of reiferon (an antiviral IFN) intramuscularly 3 times a week. The remaining patients received basic therapy aimed at improving bile secretion (holoasa or hophitol) and liver function (riboxin per os). Identical immunocorrecting effects were registered in the patient group receiving TF PLUS for 2 weeks and in the patients, receiving IFN therapy for 3 months. In the patients receiving TF PLUS there were earlier symptoms dynamics that were positive. TF PLUS was well tolerated and there were no side effects as compared with fever, joint pain and asthenia during interferon therapy. It is worth pointing out that the incidence of viral remission in the groups receiving reiferon and TF Plus was the

same, i.e. 65%. At the same time the level of g-interferons production was significantly higher in the patients receiving TF Plus.

The effectiveness of TF and TF PLUS in the treatment of viral hepatitis B and C may be of great help in considering the use of the TF products as the alternative treatment in recombinant interferons or as an addition to the conventional therapies for viral hepatitis.

The data obtained indicates further studies of the effectiveness of TF products should be conducted to additional patients in order to develop the most effective schemes of complex treatment, pharmacologically effectiveness, the dose courses and the economics.

The Use of TF in Chlamydial Infections

In recent years chlamydial infection has become a serious health care problem. The majority of reports of domestic as well as foreign authors are dedicated to urogenital chlamydiosis (40, 52). The use of modern antibiotics leads to the development of such side effects as dysbacteriosis, toxic liver lesions, and secondary immunodeficiencies. When developing therapeutic measures one must bear in mind the cycle of chlamydia development, the possibility of L-forms formation (lacking a cell wall), and its perseverance in the body that necessitate not only the correct choice of antibiotics but the search for effective immunocorrecting agents (6). The use of TF and TF PLUS in the treatment of urogenital chlamydiosis in adult patients is of great interest (22, 26).

Twenty-four (24) male patients with urogenital chlamydiosis received antibacterial therapy according to the traditional scheme for a month (10 days each of clarythromycin, doxycyclin and ofloxacin). The second group (26 patients) received one 10 day course of clarythromycin and in addition TF PLUS, 1 capsule 3 times daily for the 10 days. The third group (23 patients) received clarythromycin and TF according to the same scheme. The examination of urethral smear and prostate secretion using the Polymerase Chain Reaction (PCR) DNA method two months after the end of the treatment registered 100% chlamydia eradication in all three groups.

Seventy-two percent (72%) of patients that received traditional antibacterial treatment complained of discomfort in the epigastric area and one third (32%) complained of nausea. There were cases of vomiting (12%) and dyspepsia (12%). Intestinal dysbacteriosis with the prevalence of fungal lesion and genital candidosis were registered in 88% of the cases. From antibacterial therapy there were hepatotoxic effects such as jaundice syndrome (8%), liver enlargement (17%) and increased activity of hepatic enzymes (54%). All these manifestations necessitated additional therapies such as the use of enzymes and other bioagents, additional agents for improving hepatic function, and the use of fungicides, thus prolonging the course of the treatment and increasing costs.

The first phase of specific immune defensive response is know to start with the activation of the entire cytokines complex (interleukins, interferons, adhesion molecules and etc.), i.e. monocytic-macrophagal phase activation (48, 49). The levels of IL-1b, IL-2 and IFN-g concentrations were defined before and after the treatment in 45 urogenital chlamydiosis patients. The imbalances in the cytokines studied are shown in the data. There is a statistically significant different between the concentration of the main proinflammatory IL-1b and its normal value.

IL-2 is a classic interleukin, which not only participates in the induction of cellular immunity, but also performs its main function, namely, destruction of cells altered by exogens. It also activates T-cells, NK cells as well as all cellular entities (macrophages, neutrophiles and others) that are capable of destroying diseased cells and microbes. In our studies IL-2 titers were found to be high during the first days of development of the inflammatory process. IL-2 concentrations were significantly different from its normal

concentration; while at the same time INF-g concentrations in urogenital chlamydiosis patients revealed a statistically significant decrease as compared with that of the control group.

There was no significant difference in the effects of TF or TF PLUS in either the dynamics of clinical manifestations or in the immunological shifts. This is yet another confirming fact that cytokines in these products are the major active principle and other components potentiate their effect.

Urologists may prefer TF PLUS, which would be quite understandable since it contains zinc, which produces beneficial effect on sexual function. Zinc helps prevent the formation of hypertrophic prostatic processes thus promoting a purposeful prevention of its benign enlargement.

It should be pointed out that combining interferon drugs and antibiotics in the patients with chlamydiosis (41) and leikinferon and antibiotics in children with chronic pyelonephritis (28) protects them from adverse effect of antibacterial drugs and minimizes the development of intestinal dysbacteriosis.

The combined use of interferon agents, cytokines and antibacterial therapy brings a marked therapeutic effect with lower doses of each component. The potentiating effect of cytokines allowed for both significantly decreasing the effective dose of antibiotics and minimizing their negative effect. It may be a useful strategy to use oral doses of cytokines to help patients suffering from intestinal infections and intestinal dysbiosis caused by persistent intracellular infections. TF potentiates the effect of eubiotics, enzymatic products and adaptogens.

The Effectiveness of TF Use in Osteomyelitis

Studies of the effectiveness of TF in osteomyelitis patients carried out at St Petersburg State Medical Academy (12, 13, 38, 39) revealed a diversity of its mechanistic effects.

Chronic osteomyelitis is a protracted severe infection. Free radicals and lipid peroxidation reactions play a major role in the pathogenic mechanisms of the disease and in inducing immune deficiency in patients (36, 37).

Third-three (33) patients, ages 25 to 64, with different forms of osteomyelitis were included in the study. The patients were divided into two groups. The protocol consisted of surgical removal of the purulent infection, performed a week after the beginning of TF use, and a wide spectrum antibacterial therapy (gentamycin, ampicillin and others) in post operative period.

The main group patients (20 people) were receiving TF, 2 capsules 3 times daily, along with the standard antibacterial therapy. Thirteen (13) nosology, sex and age matched people comprised the control group and received standard treatment.

It was shown that in addition to its immunomodulating effect, TF influenced the biochemical non-specific resistance mechanisms, including free radicals oxidation, increased cellular membranes stability and the antioxidant defense activity. The nature of the changes in biochemical values showed that in addition to being immunotropic, TF may also produce adaptogenic effects.

There were significant changes in humoral immunity, characterized by increased IgA production, stimulation of phagocytic immunity, as well as in the dynamics of certain T-cells populations and without a noticeable increase in circulating immune complex (CIC) level. Patients experienced clinical improvements in their condition and post-operative rehabilitation periods were shortened.

Due to its membrane stabilizing and its antioxidant effects TF can be extensively used at the beginning of a microbial-inflammatory processes (before the development of immune reactions) when adhesive processes are of consequence.

The use of TF in the patients with hematogenic osteomyelitis prompted the following method of its use both in the active phase and for immune disturbances during rehabilitation: 2 capsules 3 times daily for 2 weeks prior to surgery along with the basic therapy and for 2 months following surgery. TF is then replaced with two months of vitamin-mineral supplementation. Subsequently, after checking patient immune status and in cases of immunodeficiency TF, 1 capsule 3 times daily, should be given for 2 months and the above mentioned treatment should be repeated.

In case of immunodeficiency in other non-hematogenic forms of osteomyelitis TF, 1 capsule 3 times daily, should be taken for 2 weeks before and for two months following surgery. Following a 4-5 month break in therapy, in cases where immunodeficiency has reoccurred TF should be administered for another two months.

If remission is interrupted with an exacerbation of osteomyelitis TF, 2 capsules 3 times daily, should be taken for one week before and for one month after surgery.

The User of TF in Immunorehabilitation Therapy of HIV Infection

Acquired Immunodeficiency Syndrome (AIDS) is one of the most serious problems confronting modern medicine. For HIV patients immune modulation therapy (i.e. the restoration of normal immune function) is aimed altered immune mechanisms and at the pathogenic agent(s). The results of studies conducted (10, 11) showed that TF PLUS treatment significantly improved the immune status of HIV patients. The product also proved useful in other aspects of therapy as for example the level of circulating immune complexes (CIC) decreased to normal values in 50% of patients receiving TF PLUS.

Because the CD4 T-helper marker is a HIV receptor, whereas HIV is tropic to T-lymphocytes and other immunocompetent cells it infects mainly T-helpers while sparing cytotoxic cells. A significant increase in T-helper (CD4+) levels in patients receiving TF PLUS is an important aspect in helping to attain the main goal of such patient treatment, namely, maximum life extension and preservation of its quality.

In HIV therapy patients received TF PLUS, 1 capsule 3 times daily for two weeks. Repeated courses of TF PLUS are prescribed during the process of out-patient follow-up as based upon the investigative results of a patient's immune status.

The User of TF in the Complex Treatment of Atopic Conditions

Allergic diseases are one of the many challenges for modern medicine. Statistics from all over the world show this pathology to be skyrocketing (up to 20% of the population). Now days, one person in five on the Earth is suffering from some form of atopic pathology. According to the World Health Organization's (WHO) prognosis, atopic conditions will hold the first place in general morbidity in the 21st century. At the same time the available traditional antihistamine agents are not effective enough; their effects are limited to partial histamine receptor blockage and are often accompanied by adverse reactions. Pathogenic mechanisms of allergy development are known to be connected with a disturbance in the course of T-lymphocyte differentiation, decreased activity of the T-suppressor cells and excessive IgE production. The final link of this chain is mast cell activation and degranulation. It is necessary to find the means of influencing the various links of these atopic reactions. In our view cellular cytokines that regulate suppressor cell activity are suited best of all for this purpose.

Transfer factors used as a biologically active substance will help to modulate local (i.e. within the limits of gastro-intestinal tract) and general immune reactions of dietary allergies as well as atopic skin reactions in the diseases characterized by atopic reactions, after 20 days of the product administration all patients had remission.

Promising results were obtained from TF use in dermatovenerology (29, 30), namely, in psoriasis and atopic dermatitis patients where autoimmune and allergic reactions play important roles in the pathogenesis of these diseases (8). After 7-10 days of TF administration along with traditional drugs, patients reported less intensive itching, scaling and skin eruption.

Immunomodulating Effect of TF Use in Opisthorchiasis

The use of TF PLUS, 2 capsules 3 times daily for 7 days, in opisthorchiasis patients brought about clinical and immunological effects (920). Unlike the control group patients who received only anthelmintic treatment, patients treated with TF PLUS demonstrated a complete remission and in all patients there was a disappearance of vasculitis and arthralgia that occurred within 6 months following treatment.

Immune system indices in the patients who received TF PLUS differed significantly from those of the control group patients. Two weeks after treatment there was an increase of IgG level and more active CIC formation in the patients of TF PLUS group. Also, in the patients who received TF PLUS their concentrations of IFN-g, which plays an extremely important role in the development of a specific immune response, increased more than twofold as compared with the values before the treatment and with those of the control group (27, 34, 44). Conventional anthelmintic treatment alone did not bring about any tangible changes in the indices of the immune system humoral components studied, thus reflecting a certain unresponsive characteristic of the process.

The results of this study have convincingly shown the clinical and immunological effectiveness of TF PLUS in the complex treatment of opisthorchiasis patients. The product significantly contributed to clinical recovery of the patients during a six-month period.

TF PLUS used for immunorehabilitation, when carried out after bilthricide treatment, is of practical value in the process of forming defensive immunity. It also prompts quick elimination of *Op. felinus* antigens, arrests the development of immunopathological processes and brings about more complete and easier recovery.

The Role of TF in Immunorehabilitation of Oncology Patients

Gastric cancer is an oncological disease characterized by the development of persistently stable immunodeficiencies, which are also a consequence of the peculiarities associated with the surgical treatment of the disease.

Numerous immune condition studies of gastric cancer patients have shown that development of secondary immunodeficiency adversely affects both the adequacy and the effectiveness of immune response and shortens the duration of remission periods. These factors necessitate a complex approach to gastric cancer immunotherapy after maximum reduction of the diseased cells (25).

Twenty-five (25) patients (the treatment or main group) with second or third clinical stage of gastric cancer participated in clinical studies of TF PLUS. The studies were conducted in RAMS Cancer Research Center. Twenty-five (25) patients of sex, age, nosology, and matched disease stage comprised the control group (25). All of the gastric cancer patients in both groups underwent surgical treatment and during the post-operative period the standard procedure of immunotherapeutic treatment. To stimulate non-specific immunity, patients in the treatment group received TF PLUS, 1 capsule 3 times daily for 30 days, along with the

standard treatment. It should be pointed out that initially the majority of patients suffered from immunodeficiency of varying severity and immunodeficiency was provoked by surgery.

After the end of the course of complex treatment the study was continued with TF PLUS administration and it demonstrated that the continued treatment was beneficial to immune, interferon and cytokine status, as well as for the clinical improvement of the patients. There was an increase of CD3+, CD4+ and CD8+ content in bloody lymphocyte populations and the number of NK cells in blood samples markedly increased both showing activation of the cell mediated immunity. Concerning humoral immunity, positive charges towards normal levels of TNF-a and IL-1b production were registered.

Other positive changes characterized by decreased severity in intoxication syndrome, improved general state of being better appetite and disappearance of weakness and fatigue in the clinical course of the disease were observed. The post-operative period was uneventful. There were no reoccurrence of the disease during the course of the complex immunotherapy that was fortified by TF PLUS.

TF PLUS is well tolerated by patients and is effective as a part of a complex immunotherapy for oncology diseases and can be successfully used in clinical practice.

The Effectiveness of TF PLUS in the Complex Treatment of Duodenal Ulcer

Convincing results supporting the use of TF PLUS in a multi-faceted treatment of *Helicobacter pylori* (Hp) associated duodenal ulcer were obtained by Iu.V. Telnyikh at Moscow's Sechenov Medical Academy.

Thirty-five (35) patients with duodenal ulcer associated with Hp took part in the clinical studies. They were divided into two groups. The control group (15 patients) received Omez, Amoxicillin, and Clarythromycin according to traditional treatment in order to eradicate Hp. The main group (20 patients) received TF PLUS, 2 capsules 3 times daily for the first 10 days, then 1 capsule 3 times daily for the following 20 days along with the eradication therapy.

Laboratory results measuring humoral and cellular immunity showed that there was a pronounced immune imbalance in patients with duodenal ulcer with associated Hp disease that had persisted for more than 10 years and who had a pathological condition of the hepatobiliary system. Blood samples from these individuals showed a marked decrease in both percent and absolute number of natural killers (NK) with decreased activity, a decrease of T-helpers, and an increase of T-suppressors number which results in a decrease in the immunoregulatory index. Other authors have obtained analogous data (4, 5, 53, 55). The 10-day eradication therapy with Omez, Amoxicillin and Clarythromycin aggravated the immune imbalance leading to the development of secondary immunodeficiency due to the antibiotic's activity and its aggravation of intestinal dysbiosis.

The combination of Hp eradication therapy along with the natural immunomodulators TF PLUS brought about a marked and statistically significant improvement of both humoral and cellular immunity, which resulted in normalization of the immunoregulatory index and improved neutrophils and natural killer cell activity. The elimination of the secondary immunodeficiency by TF PLUS activity resulted in the improvement of the condition of patients with duodenal ulcers. In particular, the effectiveness of eradication therapy was increased by 21.7%, pain and dyspeptic syndromes, respectively, were arrested 4 and 4.5 days earlier and mucosal ulcer scarring occurred 8 days earlier in the TF PLUS treatment group as compared with the control group. Eradication of Hp was 73.3% successful in the control group. Eradication of Hp in the group receiving TF PLUS was 95%.

The clinical data obtained and the data from other authors show the usefulness of TF and TF PLUS in various infectious and somatic pathologies.

5. Methods of Transfer Factors Use and Recommended Doses

The developments of rational and effective regimens for the use of TF in various pathological conditions have been demonstrated. Both literature data and the results of clinical studies presented in this paper give justification for recommending regimens for TF and TF PLUS use in initial and anti-relapses of somatic and in infectious diseases (table 1).

The conventional scheme of TF use is:

- For the prevention of seasonal diseases (spring, autumn) connected with the weakening of the immune system – 1 capsule 3 times daily for 30 days;
- In acute infections at the beginning of a disease - 2 capsules 3 times daily for not less than 7 days.

Table 1. Schemes of the use and average course doses of TF and TF Plus (TF+) in various diseases in adult patients.

Disease	Treatment Procedures	Dose	Duration of a Treatment
1	2	3	4
HIV Infection	TF+	1 capsule 3 times daily	14 days repeated courses with immunogram monitoring
Acute Viral Hepatitis B (sluggish or protracted course)	TF	1 capsule 3 times daily	14 days individual repeated courses during follow-up study
Chronic viral hepatitis B and C	TF or TF+	1 capsule 3 times daily	For 14 days each month for the first three months. Repeated courses for 14 days, 1 capsule 3 times daily, monitored by biochemical analyses, liver ultrasound investigation once every 2-3 months.
Hematogenic Osteomyelitis & immunodeficiency – 1st Type	TF and basic antibacterial therapy	2 capsules 3 times daily	14 days before surgery and 2 months after surgery
In case of immunodeficiency persistence after a 2 month treatment	TF	1 capsule 3 times daily	Two months
Chronic Osteomyelitis aggravation	TF and basic treatment	2 capsules 3 times daily	1 week before surgery and 1 month after surgery
Opisthorchiasis	TF or TF+ After anthelmintic treatment and bilthricide	1-2 capsules 3 times daily	7 days repeated courses in case of persistence of immunopathological processes manifestations (arthralgia, vasculitis)
Acute Urogenital Chlamydiosis	TF+ and antibiotic	1 capsule 3 times daily	10 days
Chronic Urogenital Chlamydiosis (complaints & clinical manifestations lasting for more than 2 months)	TF or TF+ and antibiotic	2 capsules 3 times daily/ 1 capsule 3 times daily	10 days 10 days and for 2 months after the end of the basic treatment (antibacterial therapy aimed at prevention of complications)
The involvement of internal reproductive organs (as complications of chronic urogenital chlamydiosis)	TF+ complex treatment along with various groups of drugs, as well as physio and restoration treatments	2 capsules 3 times daily 1 capsule 3 times daily	10 days during a process aggravation 10 days as a preventative measure the frequency of TF use depends on the extension and severity of the process, as well as the presence of a secondary immunodeficiency and as a preventative measure and varies from 2 to 4 times a year
Psoriasis, Atopic Dermatitis	TF	1 capsule 3 times daily	14-21 days; repeated courses and during unfavorable seasons of the year
Gastric Cancer after Surgery	TF+	1 capsule 2 times daily	30 days minimal frequency of repeated courses: 2 months
Duodenal Ulcer: - during eradication - after eradication - anti-relapses treatment	TF+	2 capsules 3 times daily 1 capsule 3 times daily 1 capsule 2 times daily	7-10 days until the end of a month (20-23 days) for 1 month early in spring and late autumn

6. Conclusions

Immunorehabilitation for many infectious and somatic diseases is becoming one of the most important components of successful therapies. The adaptability and frequent intracellular persistence of infectious agents, as well as the absence of an active immune reaction on the part of the individual with such diseases dictate the necessity of considering this approach. In addition, a large portion of population suffers from secondary immunodeficiencies caused by the unfavorable effects of social, ecological and other factors.

Mixed infections hold a special rank among so-called “new” infections. It is the condition when, due either to simultaneous or sequential infection by different agents, the clinical manifestations of a disease undergo significant changes. Their frequent occurrence is explained by various immunopathological conditions.

Faced with a steady increase in atopic reactions, which aggravate the course of many diseases, hamper the administration of an effective treatment, and autoimmune processes, which trigger progressive pathological conditions, physicians must not only know the basic principles of immunology but should actively seek new immunomodulating approaches for treating such conditions.

At present, the main courses of active non-specific immunotherapy are the use of interferon inducers, stimulators of macrophagal activity B and T-lymphocytes, natural and recombinant interferons with antiviral and immunomodulating effects, as well endogenous regulators of immune reactions such as interleukins and other cytokines. The use of natural endogenous non-specific immunomodulators opens up new prospects of immunorehabilitation in various infectious and somatic diseases. Generally, parenteral administration of cytokines result in pronounced proinflammatory effects leading to intensification of already hyper inflammatory reactions. In our view the use of Transfer Factor, a unique and new generation immunomodulators derived from bovine colostrum, is very promising in countering this problem.

Experimental data and the results of studies carried out in different clinics of this country have demonstrated the immunomodulating effects of oral forms of transfer factors in various infectious, parasitic and somatic diseases. According to the results of these studies, TF produced practically the same immunomodulating effect as did the most often used interferons, cytokines and other immunomodulators. In addition, oral use of TF minimizes adverse reactions, gives optimal pharmaeconomic effects and helps to shorten the course of immunorehabilitation therapy.

TF and TF PLUS have marked immunocorrecting effects and are useful for their therapeutic and prophylactic effectiveness in various forms of infectious and somatic pathologies, which are accompanied by disease induced disturbances in immune status.

7. References

1. T.I. Avdeeva, N.V. Medunitsin *et al* Interferon impact of the level of the 2 class antigens of MHC expression. *Immunology* 1987(4), p.82-85.
2. M.M. Averbakh, V.F. Salov, S.I. Agal'tsova, Prokhorov Via, Dem'ianenko NV, Apt AS. [The indices of interleukin 1, 2 and 4 production and the specific antibody titers in mice with an opposite sensitivity to staphylococcal infection] *Zh Mikrobiol Epidemiol Immunobiol.* 1996 Mar-Apr;(2):79-81.
3. G.N. Akzhigitov, M.A. Galeev, V.G. Sahautdinov, Y.B. Udin. Osteomyelitis – M., Medicine, 1986, p.23-28.
4. S.A. Alekseeieva, O.V. Krapivnaya, O.K. Komarova *et al* Life quality, clinical sumptomatology and manometric values in the patients with IBS and functional dynamics after Hp eradication Helibacter Pylory infection. Russian national congress “Man and drug” 2003, p.93.
5. V.M. Arutiunian, E.G. Grigorian. [Effectiveness of using immunomodulators in combined treatment of patients with chronic gastritis and ulcer disease] *Klin Med (Mosk).* 2003;81(5):33-5. Russian.
6. A.I. Autenshlus, O.B. Ivanova, T.N. Konovalova. The immune status of pregnant women with infectious-inflammatory diseases of urogenital localization. Novosibirsk, Russia 1998.
7. A.L. Bondarenko, S.V. Baramzina. Role of HLA phenotype in the formation of chronic HCV infection, *Epidemiology and Infectious Diseases (Epidemiologiya I infektsionnye bolezni)*, 2002, 3, p.40-42.
8. E.V. Golovina. The use of Transfer Factor in the treatment of skin diseases. *Annals of scientific conference “Immunorehabilitation in infectious inflammatory diseases”* Barnaul, November 29, 2003, p.46-49.
9. V.M. Granitov, N.V. Karbisheva, E.A. Bobrovsky, M.A. Nikulina. The Use of Transfer Factor in the treatment of chronic viral hepatitis B and C. *Annals of the 8th congress of Russian-Italian Society on Infectious Diseases.* December 5-6 2002, St Petersburg 2002, p.88-89.
10. V.M. Granitov, N.V. Karbisheva, E.U. Kozevnuikova, S.I. Belich, L.B. Sultanov. Activated transfer factor in pathogenetic treatment of HIV infection. *Annals of scientific conference “Immunorehabilitation in infectious inflammatory diseases”.* Barnaul, November 29, 2003, p.50-54.
11. V.M. Granitov, N.V. Karbisheva, L.B. Sultanov, C.W. McCausland, E.A. Oganova. The use of activated Transfer Factor in the treatment of HIV patients. *Journal HIV, AIDS and related problems.* St Petersburg 2002, v.6 (1), p.79-80.
12. V.A. Dadali, A.B. Rak, E.C. Stolpnik, C.W. McCausland, E.A. Oganova. Some new aspects of Transfer Factor effect – “Biologically active food supplements and the problem of nutrition optimization”. *Annals of 6th International symposium, Sochi, 2002,* p.62-63.
13. V.A. Dadali, A.B. Rak, E.C. Stolpnik, C.W. McCausland, E.A. Oganova. “The use of Transfer Factor in the treatment of osteomyelitis patients.” *Journal Bulletin of St Peterburg Federal Medical Academy. Named after I.I. Mechnikov* 2002 No.3-4.
14. Z.M. Dubossarskaya, V.P. Kuznetsov. Interferon in the complex treatment of patients with chronic inflammatory processes in internal genitalia. *Obstetrics and Gynecology.* 1991 Dec.(2) p.38-40. Russian.
15. K.D. Durmanov. Immunological indices in chronic osteomyelitis and their change in the course of treatment. *Kazakhstan Health Care.* 1987 (5) p.39-41.

16. E.V. Golovina. The use of Transfer Factor in dermatology. Scientific conference with international participants. "Immunorehabilitation in infectious inflammatory diseases". Barnaul, Russian, November 29, 2003, p.46-49.
17. N.I. Iluina. Secondary immunodeficiency conditions. Protocols of diagnostics and treatment. Allergy, Asthma and Clinical Immunology. 2000 (1), p.31-33.
18. N.V. Karbisheva, L.B. Sultanov, C.I. Belich. Laboratory diagnostics aimed at the evaluation of the immunorehabilitation effectiveness in opisthorchiasis patients. Scientific conference with international participants "Immunorehabilitation in infectious inflammatory diseases". Barnaul, Russian, November 29, 2003, p.42-45.
19. N.V. Karbisheva, P.B. Tatarinstev, V.M. Granitov, I.A. Karbisheva, C.W. McCausland, E.A. Oganova. Transfer Factors in the treatment of viral hepatitis patients. Annals of International conference. Banraul, Russia, November 29, 2003, p.29-32.
20. N.V. Karbisheva, C.W. McCausland, E.A. Oganova. Clinical and immunological effectiveness of Transfer Factor Plus in the treatment of chronic opisthorchiasis patients. Scientific conference with international participants "Immunorehabilitation in infectious inflammatory diseases". Barnaul, Russia, November 29, 2003, p.42-45.
21. N.V. Karbisheva, I.A. Karbisheva, P.B. Tatarinstev, C.W. McCausland, E.A. Oganova. The use of Transfer Factors in the treatment of viral hepatitis patients. Siberian Journal of Gastroenterology and Hepatology. 2003 (16), p.147-149.
22. N.V. Karbisheva, D.V. Kipriyanov. A report on the results of TF Plus use in the treatment of urogenital chlamydiosis patients. Altay State Medical University, 2003.
23. K.P. Kashkin. The immune system cytokines: the main properties and immunobiological activity (a lecture). Clinical and Laboratory Diagnostics, 1998, (11), p.21-32.
24. C.A. Ketlinsky, A.S. Simbirtsev, A.A. Vorobiev. Endogenous immunomodulators, St. Petersburg Hippocrates, 1992.
25. M.V. Kisielevsky, E.O. Khalturina. The use of Transfer Factor Plus in the treatment of gastric cancer patients. Scientific conference with international participants "Immunorehabilitation in infectious inflammatory diseases". Barnaul, Russia, November 29, 2003, p.33-38.
26. D.V. Kipriyanov. The results of Transfer Factor Plus use in the treatment of urogenital chlamydiosis. Scientific conference with international participants "Immunorehabilitation in infectious inflammatory diseases". Barnaul, Russia, November 29, 2003, p.39-41.
27. A.T. Kotelkin. Looking for the ways of the studying of *Opisthorchis felinus* markers and the study of their use for opisthorchiasis diagnostics. Abstract of doctoral dissertation. Koltsovo, 2000, 20 pages.
28. G.M. Letifov. The role of sensitivity to gram-negative bacteria endotoxins in pyelonephritis pathogenesis in children. (clinical-experimental study). Dissertation doctoral. Rostov-on-the-Don. 2000, 450 pages.
29. S.G. Lyikova, O.B. Memchaninova, E.B. Chernikova, U.P. Gichev. The use of Transfer Factor in dermato-venerology Siberian Journal of dermato-venerology. 202 (3), p.34-35.
30. S.G. Lyikova, O.B. Memchaninova, E.B. Chernikova, U.P. Gichev, A.N. Trunov. The use of Transfer Factor in dermato-venerology. Annals of VI International symposium. "Biological active substances to the food and problems of the optimization of nutrition" Sochi, November 5-7, 2002, p.146-147.
31. A.N. Mats. Transfer factor products as the means of a specific immunotherapy. Medical immunology, 2001, v.3 (2), p.328-329.
32. E. Oganova, C.W. McCausland, W.J. Hennen. Transfer Factors – new generation of biologically active dietary supplements. Annals of VI International symposium "Biological active substances to the food and problems of the optimization of nutrition" Sochi, November 5-7, 2002, p.192-193.

33. E. Oganova, C.W. McCausland. Transfer Factors – natural immunocorrectors. Scientific conference with international participants “Immunorehabilitation in infectious inflammatory diseases”. Barnaul, Russia, November 29, 2003, p.22-26.
34. H.H. Ozeretskoykaya, E.E. Chuikina, C.B. Parfenov. 1. Tolerance to opisthorchia antigens: immunity or genetics? Opisthorchiasis. Annals of a conference. Tumen, 1991, p.171-174.
35. R.V. Petrov, P.M. Chaitov, B.V. Pinegin. The evaluation of human immune status in normal condition and in pathology. Immunology. 1994 (6), p.6-9.
36. A. Right. Basics of Immunology. Translation from English by M. Mir, 1998, p.86-100.
37. B.V. Pinegin. Immunodiagnostics and immunotherapy of surgical infections. International Journal on Immunorehabilitation, 1998 910), p.86-100.
38. A.V. Rak, E.C. Stolpnik, V.A. Dadali, G.A. Baskovich, C.W. McCausland, E A. Oganova. The study of the possibility of transfer factor use in purulent surgery. Annals of international congress “Traumatology and orthopedics present and future”. Moscow, April 7-9, 2003.
39. A.V. Rak, V.A. Dadali, E.C. Stolpnik, C.W. McCausland, E A. Oganova, L.B. Gaikovaya. Immunological indices in chronic osteomyelitis patients in the course of treatment with the use of transfer factor. Annals of a scientific conference with international participants “Immunorehabilitation in infectious inflammatory diseases”. Barnaul, Russia, November 29, 2003, p.55-60.
40. A.P. Remezov, V.A. Neverov. Chronic chlamydial urogenital infection. Terra Medica. 1996 (4), p.36-38.
41. Iu.E. Serebryansky, C.C. Afanasiev, L.A. Denisov, O.B. Rubalsky. Cytokines in infected patient’s immunorehabilitation. Military Medical Journal, 1999, v.320 (3), p.41-50.
42. V.V. Sokolovsky. Thiolsulfide blood ratios as an index of non-specific body resitsnaces. St Petersburg, Russia. 1996.
43. S.N. Sorinson. Viral hepatitis. Teza, 2nd edition, St Petersburg, Russia. 1998, p.1-308.
44. T.F. Stepanova, N.I. Skarednov. Clinical rehabilitation in the complex of measures aimed at opisthorchiasis control. Opisthorchiasis. Annals of a conference, Tumen, 1991, p.232-234.
45. B.P. Sukhanov. Transfer Factors as a part of human nutrition. Annals of a scientific conference with international participants “Immunorehabilitation in infectious inflammatory diseases”. Barnaul, Russia, November 29, 2003, p.27-28
46. W.J. Hennen. Transfer Factor Plus: an ideal combination of biologically active substances for optimal immunity. (Editors U.P. Gichev, E.A. Oganova). Novosibirsk, 2001, 73 pages.
47. A.S. Khabarov, S.S. Dergachev. Immunorehabilitation of descendants of the second generation irradiated at Semipalatinsk testing area. Annals of a scientific conference with International participants “Immunorehabilitation in infectious inflammatory diseases”. Barnaul, Russia, November 29, 2003, p.18-19.
48. R.M. Khaitov, B.V. Pinegin. The main principles of immunomodulating therapy. Allergy, asthma and clinical immunology. 2000 (10), p.9-16.
49. R.M. Khaitov, B.V. Pinegin. Modern understanding of body defense against infections. Immunology. 2000 (1), p.61-64.
50. A.A. Yarinin. Modern problems of allergology, clinical immunology and immunopharmacology. Annals of the 1st national conference of Russian Association of Allergologists and Clinical Immunologists. January, 28-31, 1997, Moscow, M. p.161-167.
51. V.A. Danis, G.M. Franic, D.A. Rathjen, P.M. Brooks. Effects of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha) and IL-6 on the production of IL-1 and TNF-alpha by human monocytes. Clin. Exp. Immunol. 1991, Jul; 85 (1), p.143-50.

52. C. De Punzio, E. Neri, P. Metelli, M.S. Bianchi, M. Campa, P. Fioretti. Epidemiology and therapy of chlamidia trachomatis genital infection in women. I. Chemother. 1991, Jun; 4(3), p.163-6.
53. M.B. Grisham, M.W. Owens. Cytokines increase proliferation of human intestinal smooth muscle cells: possible role in inflammation-induced stricture formation. Inflammation. 1993, Aug; 17(4), p.481-7.
54. H.S. Lawrence, W. Borkowsky. Transfer Factor – current, status and future prospects. Biotherapy. 1996; 9(1-3), p1-5.
55. C. Matushansky. Circulation entero-systemique des-lymphocytes domiciliation a lamaquens'e intestinale et malasies inflamatoires chroniques de lintestin. Med.Sci. 1994, 10, p.8-9.
56. W.E Paul, R.A. Seder. Lymphocyte responses and cytokines. Cell. 1994, Jan 28; 76 (2), p.241-51.