Clinical Efficacy of Systemic Enzyme Support

Joseph J Collins, RN, ND

Clinical observations and literature review both affirm the conviction that systemic enzyme support with Wobenzym® N or Wobenzym® PS is an essential component for successful management of inflammation disorders and other conditions with immune system dysregulation due to its high degree of clinical efficacy. In addition to improving clinical outcomes in conditions with overt inflammation, such as rheumatoid arthritis, thrombophlebitis, pyelonephritis, prostatitis and psoriasis, systemic enzyme support is also affective in conditions with covert inflammation such as osteoarthritis, angina, atherosclerosis, myocardial infarctions, and diabetes to name a few. The adjuvant properties of systemic enzyme support have also been observed and documented for a number of cases including adnexitis, arthritis, papillomas and various forms of cancer. This article will familiarize clinicians with the therapeutic benefits of systemic enzyme support and review pertinent findings related to this treatment modality.

Enzymes are biological molecules that increase the rate of chemical reactions. In the human body, thousands of chemical reactions occur during the course of normal metabolic processes. These reactions require significant energy in order to take place. Enzymes act as catalyst to lower the energy needed for the reaction to move forward. As such, enzymes maintain optimal function of the various systems in the body and support overall good health and optimal quality of life.

The immune system is very dependent on proper enzyme function in regards to regulating inflammation as well as protecting cells from damage. Cytokine activity, and the clearance of excessive inflammatory cytokines, is regulated by proteases, enzymes which degrade proteins. The clearance of tissue proteins and peptides damaged by inflammation is also mediated by proteases. Proteases significantly reduce concentrations of advance glycation end-products (AGEs) and protect cells by decreasing their receptor (RAGEs) activation. Proteases also down-regulate adhesion molecule activity in inflamed, as well as malignant cells.

Inflammation Observed

This inflammation response can be quite aggressive, and manifest as the five cardinal signs of inflammation recognized ages ago: redness, heat, swelling, pain and loss of function, classically referred to in Latin as *rubor, calor, tumor, dolor & functio laesa*. Pain, loss of function, and other cardinal signs of inflammation diminish our quality of life and may be a harbinger of serious disease. Therefore, clinically evident inflammation is often recognized as the body communicating an inability to control proper cellular processes.

In addition to the clinical signs of inflammation, laboratory tests often show increased levels in the various biomarkers of inflammation that are also associated with increased morbidity and mortality. These include the well known erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP). Circulating

Immune Complexes (CICs), and immunoglobulins (IgG, IgE, IgA & IgM) are often elevated by excessive inflammation. Excessive fibrin activity and increased amyloid beta-peptide can also be quantified in the presence of imbalanced inflammation. Certain cytokine levels may also increase, which may cause further imbalance in the immune system.
The change in certain cytokine levels is of specific interest because it allows us to recognize when the immune system has become significantly imbalanced, and provides us with insight into how immunomodulation can be achieved through the use of systemic enzymes.

Inflammation & Cytokines

Cytokines are signaling proteins and glycoproteins involved in cellular communications that play a dominant role in maintaining the normal inflammatory processes of the immune system. Cytokines such as interferon-gamma (INF-γ), tumor necrosis factor-alpha (TNF-α), transforming growth factor beta (TGF-β) and interleukins (IL-2, IL-6, IL-12, IL-4, IL-5, IL-10) are produced de novo (on demand) in various cells as a direct response to stimulation of the immune system. They are produced by a wide variety of cells

and are typically subdivided into two categories, Th1 & Th2. A balance between Th1 and Th2 responses is best for optimal health.
Th1 cytokines tend to produce the pro-inflammatory responses involved in antibacterial, antiviral and antifungal responses. Excessive Th1 responses can lead to uncontrolled tissue damage and may perpetuate autoimmune responses. A relative excess in Th1 is also observed in acute inflammation.Th2 cytokines tend to produce anti-inflammatory responses and can counteract the Th1 mediated microbicidal actions. Excessive TH2 responses are associated with allergies and atopy (asthma, eczema, allergic rhinitis & allergic conjunctivitis). A relative excess in Th2 is also observed in chronic inflammation.
The binding and removal of excessive cytokines is mediated by α-2-macroglobulin (alpha 2-macroglobulin), a naturally occurring high molecular weight plasma glycoprotein. Proteases bind with α-2-macroglobulins to create α-2-macroglobulin-protease complexes[1,2] and transform the α-2-macroglobulin from its native form into the active form. Systemic enzyme support increases endogenous proteases and supports the activation of α-2-macroglobulin.
The newly activated α-2-macroglobulin-protease complex now has increased binding capacity for certain cytokines[3], as well as other proteins and glycoproteins. Protease activation of α-2-macroglobulin also facilitates its binding to, and elimination of, proteins damaged by oxidative stress or heat[4] as well as the degradation and clearance of the amyloid beta peptide (A beta), a major component of senile plaques in Alzheimer's patients.[5-10]
These activated alpha 2-macroglobulin-proteinase complexes, which now bind excessive cytokines and damaged proteins, are also activated for receptor mediated endocytosis when they were transformed by the protease enzymes. Therefore, these complexes, as well as the cytokines and debris they carry, are quickly removed by hepatic α-2M-receptors (α-2M-R)5, and other cells expressing α-2M-R, such as macrophages.[11,12] The removal of damaged proteins, cellular debris, and unwanted peptides (such as amyloid beta peptides) are normal immune system responses to defend the body from all pathogenic influences – whatever their origin – whatever their size.

Since excessive cytokines are involved in auto-aggressive inflammatory processes, the binding to cytokines and the removal of cytokines by the activated α-2- macroglobulin proteins support a balanced and properly functioning immune system. Therefore the removal of excessive cytokines allows the immune system to restore Th1/Th2 balance. Once cytokine levels are restored to their optimal physiologically balanced state the immune system is able to resume its function of protecting the body and initiating the healing process. With renewal of the normal inflammatory process the regenerative processes of the immune system are again allowed to function.

Restoring Immunostasis

As noted, the clearance of excessive cytokines, the clearance of proteins and peptides damaged by inflammation, the inactivation of advance glycation end-products, and the inactivation of adhesion molecules in inflamed and malignant cells are all mediated by proteolytic enzymes. A balanced immune system – immunostasis – can be manifested by using systemic enzyme support, which provides the essential proteolytic enzymes. Systemic enzyme support can be defined as a treatment modality which uses oral administration of exogenous hydrolytic (mainly proteolytic) enzymes of animal origin (trypsin, chymotrypsin) and plant origin (bromelain, papain) in the form of enteric-coated tablets for supporting healthy and normal inflammatory processes in the body.

Systemic enzyme support (SES) which uses Wobenzym® N and Wobenzym® PS - clinically validated formulations of enzymes from both plants and animals - is able to influence immunity in such a fashion as to reduce pain, swelling, inflammation, edema and lymphedema, and increase fibrinolysis, and the clearance of harmful immune complexes that are a result of antibody reactions. SES provides enzymes which can be utilized to assist the body's various regulatory and communications systems and supports the function of tissues at a cellular level. SES has application for degenerative diseases, autoimmune diseases, and as an adjuvant to improve efficacy of anti-infectives in infectious diseases.

A significant amount of the published international literature describing the clinical benefits of systemic enzyme support is based on various systemic enzyme support formulations made for many decades by MUCOS Pharma, a Germany pharmaceutical company. Even after the sale of MUCOS Pharma, Wobenzym® N is still manufactured in Germany, but is distributed by MUCOS, LLC, an American company.

The history of Wobenzym® is significant in that systemic enzyme support requires sophisticated processing techniques to be effective. Systemic enzyme support formulations are considered prescription drugs in part of Europe, and manufactured to the same high standards of pharmaceuticals. The Wobenzym® N and Wobenzym® PS enteric coated, animal enzyme, plant enzyme and rutosid combinations are the most researched systemic enzyme formulations in the world; and used by athletes, doctors and millions of people to help normalize inflammation, speed recovery from sports and other routine injuries, and promote healthy circulation.

The active constituents in Wobenzym® N and Wobenzym®PS are delivered through tablets that have a special enteric coating which can withstand the acid environment in the stomach, which is important since enzymes can be damaged by stomach acid. Once the tablet has passed a safe distance from the

stomach acids, the tablet dissolves and the enzymes are efficiently absorbed by the mucosal membrane of the intestine. This process is most effective if the tablets are taken away from meals.

Conditions Treated with Systemic Enzyme Support

Based on clinical observations and literature review systemic enzyme support effectively improves the treatment of conditions with an auto-aggressive component by promoting the decomposition and elimination of disease associated circulating immune complexes. Improvements in CRP, ESR and other biomarkers of inflammation are also noted. Clinical improvement is noted in a wide range of conditions, with benefits observed in treating various body systems.

Nervous system disorders such as multiple sclerosis showed a decreased number and duration of attacks because of decreased inflammatory activity due to systemic enzyme support.[13-15] A notable increase in the degradation and clearance of the amyloid beta (A beta) peptide can reduce the risk of developing Alzheimer's disease.[16-21]

The cardiovascular system benefits by reduced risks of re-infarction after an MI because of the hypolipidemic and immunonormalizing benefits of systemic enzyme support.[22-24] Patients with stable angina pectoris had a demonstrable reduction in the frequency and intensity of angina pectoris attacks and increased tolerance of physical work load with systemic enzyme support.[25]

Disease of venous system, including acute thrombophlebitis and postthrombophlebitic syndrome were dramatically improved by systemic enzyme support, with a notable decrease of pain, reduction of edema and trophic ulcers.[26-29] Other research showed highly effective resolution of lymphedema in both upper and lower extremities due to fibrinolytic & antiedematous effects of systemic enzyme support.[33-36]

Respiratory system health is improved by systemic enzyme support with a notable reduction of both frequency and severity of recurrent respiratory tract infections. Researchers have concluded that systemic enzyme support represents a novel therapeutic modality helping in the treatment of children showing a high sickness rate and note that the as number and severity of dyspnea attacks decreased in children with proven asthma.[37,38]

Integumentary conditions had improved clinical success when systemic enzyme support was added as an adjuvant with other conventional therapies. The inclusion of systemic enzyme support in treatment of psoriasis significantly decreases the exudative component of exacerbation, increased regression and decreases recurrence.[39] Eczema (atopic dermatitis) treated with only systemic enzyme support was able to reduce skin itching manifestations, and in combination with basic conventional therapies it provided an marked acceleration of the desirable effects.[40]

Urinary system condition improvement due to treatment with systemic enzyme support include a major improvement in relapsing urinary tract infections, decreased recurrence of kidney stones and decreased progression of diabetic nephropathy. There are also positive clinico-laboratory results, which considerably exceeded those in conventional drug treatment in patients with pyelonephritis.[41-45]

Reproductive health, women's health, men's health and thyroid health conditions can all be more effectively managed by the use of systemic enzyme

support. It is an important part of the complex therapy of male and female sterility, recurrent miscarriages and chronic infections of the reproductive system. Systemic enzyme support is an effective immunomodulator for both autoimmune & alloimmune infertility.[46-48] In women, it is effective for treatment in chronic pelvic inflammatory disease (PID) and as adjuvant in treatment of acute adnexitis.[49-50] In men, systemic enzyme support is a very efficient therapy for both bacterial and abacterial prostatitis, as well as associated sexual dysfunction.[51-53] Systemic enzyme support is also a very effective therapy for the management of fibrocystic breast disease and does not interfere with already upset hormonal balance.[54-56] Autoimmune thyroid disease treated with systemic enzyme support resulted in a significant decrease of TSH, anti-TG & anti-TPO and allowed the lowering of L-thyroxine dosages.[57]
Joint health is profoundly improved by systemic enzyme support. It is an effective and safe alternative to NSAIDS in the treatment of painful episodes of osteoarthritis of the knee and hip.[58-60] Systemic enzyme support protects and preserves joint cartilage significantly better than NSAIDs in rheumatoid arthritis.[61-71] Gout therapies are significantly improved by the addition of systemic enzyme support.[72] The addition of systemic enzyme support improved both articular signs and extra-articular manifestations in the majority of the children with juvenile chronic arthritis and was able to help limit the use of corticosteroids in some children. In addition to osteoarthritis, rheumatoid arthritis, gouty arthridities, and juvenile arthritis, systemic enzyme support has also been shown as effective in the treatment of psoriatic arthritis. It is fair to say that systemic enzyme support could be used in any form of arthritis.
Sports medicine is another area in which systemic enzyme support excels. Sport & exercise related muscle pain & inflammation provoked by a strong physical tension, excessive training and heavy competition rate are decreased with “excellent results” due to the selective interferences of enzymes with the pathophysiologic mechanisms of exercise induced inflammation.[73] A prophylactic administration of systemic enzyme support in top athletes who are at risk of injury results in significantly reduced duration of injury symptoms and in absence from training and work due to such injuries. Systemic enzyme support also improves recovery from sprains, as well as shortened recovery from sport injuries severe enough to also require surgery.[74-77]

Biomarkers of Inflammation & Systemic Enzyme Support

It is again important to note that the studies showing clinical efficacy in the aforementioned conditions are based on the enteric coated polyenzyme formulations which originated from Germany. Clinicians can be confident that they will observe the same degree of clinical efficacy with Wobenzym® N, and Wobenzym®PS, which are manufactured in Germany by that company. As well as the clinically observable benefits, systemic enzyme support improves the levels of a number of biomarkers of inflammation as mentioned above.
Systemic enzyme support resulted in improvement or normalization in a number of biomarkers of inflammation. The decreased circulating immune complex (CIC) levels resulted in significant improvement in a wide range of conditions including rheumatoid arthritis, atherosclerosis, atopic dermatitis, Behçet's disease, chronic hepatitis, diabetes mellitus, and myocardial infarction.[78-87].
Decreased erythrocyte sedimentation rate was observed in urinary tract infections, adnexitis, rheumatoid arthritis, and surgical cases.[88-93] Decreased C-

reactive protein (CRP) levels in lymphedema, rheumatoid arthritis, psoriatic arthritis and surgical cases was associated with improved clinical outcomes.[94-96] The normalization of cytokine levels after tissue injury and inflammation was observed in rheumatoid arthritis and angina pectoris treated with systemic enzyme support.[97-100] Normalization of immunoglobulins (IgG, IgE, IgA, IgM) is observable in treated cases of atopic dermatitis, recurrent infections of respiratory tract and rheumatoid arthritis.[101-103] The restoration of normal fibrinolytic properties by systemic enzyme support is considered as vital for disease state management in rheumatology, immune complex diseases, traumatology, surgery, oncology, inflammations and vascular diseases as well as diseases with an infection component.[104,105] Systemic enzyme support can also up-regulate amyloid beta catabolism and reduce the risk of developing Alzheimer's disease by preventing amyloid beta accumulation in brain and vasculature.[106-111]

Clinical Conclusions

Systemic enzyme support has been demonstrated to be an effective treatment either as the primary therapy, or as an adjuvant therapy which improves clinical outcomes of diseases which are difficult to manage. Systemic enzyme support has been reported to have excellent tolerance and superior safety when compared to some conventional therapies.[112-116] The safety and efficacy of systemic enzyme support is coupled with a consumer loyalty rate of over 80 percent. This significant compliance to systemic enzyme support is believed to be primarily due to its effectiveness

Published international literature describing the clinical efficacy of systemic enzyme support is based on formulations made by a Germany pharmaceutical company. Wobenzym® N is manufacture by that same company, and available throughout the United States. Clinical observations and literature review both affirm the conviction that Wobenzym® N is an essential component for successful management of inflammation disorders and other conditions with immune system dysregulation due to its high degree of clinical efficacy.

More information can be found at **www.SystemicEnzymeSupport.org**, a non-commercial a health education and wellness promotion website dedicated to teaching the clinical efficacy of systemic enzyme support.

References

[1] - Gonias SL, Pizzo SV. Conformation and protease binding activity of binary and ternary human alpha 2-macroglobulin-protease complexes. J Biol Chem. 1983 Dec 10;258(23):14682-5.

[2] - Mettenburg JM, Gonias SL. Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes. Protein J. 2005 Feb;24(2):89-93.

[3] - LaMarre J, Wollenberg GK, Gonias SL, Hayes MA. Cytokine binding and clearance properties of proteinase-activated alpha 2-macroglobulins. Lab Invest. 1991 Jul;65(1):3-14.

[4] - French K, Yerbury JJ, Wilson MR. Protease activation of alpha2-macroglobulin modulates a chaperone-like action with broad specificity. Biochemistry. 2008 Jan 29;47(4):1176-85.

[5] - Lauer D, Reichenbach A, Birkenmeier G. Alpha 2-macroglobulin-mediated degradation of amyloid beta 1--42: a mechanism to enhance amyloid beta catabolism. Exp Neurol. 2001 Feb;167(2):385-92.

[6] - Qiu WQ, Borth W, Ye Z, Haass C, Teplow DB, Selkoe DJ. Degradation of amyloid beta-protein by a serine protease-alpha2-macroglobulin complex. J Biol Chem. 1996 Apr 5;271(14):8443-51.

[7] - Du Y, Ni B, Glinn M, Dodel RC, Bales KR, Zhang Z, Hyslop PA, Paul SM. alpha2-Macroglobulin as a beta-amyloid peptide-binding plasma protein. J Neurochem. 1997 Jul;69(1):299-305.

[8] - Hughes SR, Khorkova O, Goyal S, Knaeblein J, Heroux J, Riedel NG, Sahasrabudhe S. Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3275-80.

[9] - Mettenburg JM, Gonias SL. Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes. Protein J. 2005 Feb;24(2):89-93.

[10] - Qiu Z, Strickland DK, Hyman BT, Rebeck GW. Alpha2-macroglobulin enhances the clearance of endogenous soluble beta-amyloid peptide via low-density lipoprotein receptor-related protein in cortical neurons. J Neurochem. 1999 Oct;73(4):1393-8.
[11] - Misra UK, Sharma T, Pizzo SV. Ligation of cell surface-associated glucose-regulated protein 78 by receptor-recognized forms of alpha 2-macroglobulin: activation of p21-activated protein kinase-2-dependent signaling in murine peritoneal macrophages. J Immunol. 2005 Aug 15;175(4):2525-33.
[12] - Feldman SR, Ney KA, Gonias SL, Pizzo SV. In vitro binding and in vivo clearance of human alpha 2-macroglobulin after reaction with endoproteases from four different classes. Biochem Biophys Res Commun. 1983 Jul 29;114(2):757-62.
[13] - Mertin J.1, Stauder G., ESEMS working group. Use of oral enzymes in multiple sclerosis patients. Inter. Journal of Tissue Reactions 1997, Vol. XIX , No.1/2, pp 95.
[14] - Hana Krejcová. Wobenzym® and Wobe-Mugos® in the Treatment of Multiple Sclerosis. PharmaScript, Kathi-Kobus-Steig 1, D-82515 Wolfratshausen, Germany.
[15] - Stauder G., Donnerstag B., Baumhackl U., Buschmans E. Use of oral enzymes in multiple sclerosis: phenotyping of peripheral blood lymphocytes from MS patients under long-term treatment with orally administered hydrolytic enzymes. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp 135-137.
[16] - Lauer D, Reichenbach A, Birkenmeier G. Alpha 2-macroglobulin-mediated degradation of amyloid beta 1--42: a mechanism to enhance amyloid beta catabolism. Exp Neurol. 2001 Feb;167(2):385-92.
[17] - Qiu WQ, Borth W, Ye Z, Haass C, Teplow DB, Selkoe DJ. Degradation of amyloid beta-protein by a serine protease-alpha2-macroglobulin complex. J Biol Chem. 1996 Apr 5;271(14):8443-51.
[18] - Du Y, Ni B, Glinn M, Dodel RC, Bales KR, Zhang Z, Hyslop PA, Paul SM. alpha2-Macroglobulin as a beta-amyloid peptide-binding plasma protein. J Neurochem. 1997 Jul;69(1):299-305.
[19] - Hughes SR, Khorkova O, Goyal S, Knaeblein J, Heroux J, Riedel NG, Sahasrabudhe S. Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3275-80.
[20] - Mettenburg JM, Gonias SL. Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes. Protein J. 2005 Feb;24(2):89-93.
[21] - Qiu Z, Strickland DK, Hyman BT, Rebeck GW. Alpha2-macroglobulin enhances the clearance of endogenous soluble beta-amyloid peptide via low-density lipoprotein receptor-related protein in cortical neurons. J Neurochem. 1999 Oct;73(4):1393-8.
[22] - Sledzevskaya I.K., Loboda M.V., Kolesnik E.A., Babiy L.N., Fisenko L.I. Systemic enzyme treatment as a method of secondary prevention in patients after myocardial infarction in the rehabilitation period. II Mediterranean Congress of Physical Medicine and Rehabilitation, 20-23 May, 1998, Valencia, Spain. Abstracts- pp. 137 489 KA (19-08-3).
[23] - Sledzevskaja U. K., Šumakov V. A., Bratus V. B., Babij A., Malinovskaja U. Z., Gavrilenko T. U., Terzov A. U. Systemic enzyme therapy in the treatment of patients with myocardial infarction. Žurnal praktièeskogo vraèa 1997, No. 3, pp. 43 – 44.
[24] - Kovalenko V.N., Sledzevskaya I.K., Ryabokon E.N., Gavrilenko T.I., Terzov A.I. N.D. Strazhesko New approaches to modern cardiology based on systemic enzyme therapy. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 101-111.
[25] - Mazurov V.I., Stolov S.V., Linetskaya N.E., Onyschenko E.F. Systemic enzyme therapy in the complex treatment of angina pectoris. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 113-120.
[26] - Kopadze, T.Sh., Natsvlishvili, G.A., Tvaladze, M.G., Avazashvili, D.N. Application of Wobenzym and Phlogenzym to the angiology and vascular surgery. Georgian Medical News 2001, No. 2, (serial No.71), pp. 27 – 29.
[27] - Koshkin V.M., Kirienko A.I., Leontjev S.G., Agafonov V.F. Systemic enzyme therapy of lower limb postphlebitic syndrome. Angiology and vascular surgery 2000, Vol. 6, No. 2, pp. 61 – 64.
[28] - Džupina A., Džupinová M. Wobenzym in the treatment of Thrombophlebitis. Praktická flebologie 1998, Roè. 7, è. 1, str. 28-30 (17-12-3).
[29] - Valery M. Koshkin, M.D., D.M.Sci.Wobenzym® in the Treatment of Acute Thrombophlebitis. PharmaScript, Kathi-Kobus-Steig 1, D-82515 Wolfratshausen, Germany.
[30] - Wald M. Diagnosis and treatment of lymphedema. Interní medicína pro praxi 2003, č. 8, str. 415-417.
[31] - Kafková H., Kojanová M. Lymphedema. Postgraduální medicína 2003, 5 (6), pp. 626 – 633.
[32] - Dzupina A., Morvay P., Dzupinova M. Systemic enzyme therapy and complex decongestive therapy in the patients with primary and secondary lymphedema of lower extremity. Lymfo 2000, Praha 13. - 14. 10. 2000. Praktická flebologie - supplement 2000, Roè. IX, str. 23-27. (17-13-2)-(17-12-1).
[33] - Dusková M, Wald M. Orally administered proteases in aesthetic surgery. Aesthetic Plast Surg. 1999 Jan-Feb;23(1):41-4.
[34] - Dzupina A., Morvay P., Dzupina M. Proteolytic enzymes in lymphedema therapy. 41st Annual World Congress - ICA'99, International College of Angiology, Sapporo, Japan, July 3-10, 1999, Scientific Posters pp. 76.
[35] - Korpan MI, Fialka V. Wobenzyme and diuretic therapy in lymphedema after breast operation. Wien Med Wochenschr. 1996;146(4):67-72; discussion 74.
[36] - Kasseroller R., Wenning H.G. Efficacy and tolerability of proteolytic enzymes as an anti-inflammatory agent in lymphoedema after axillary dissection due to mammary cancer. The European Journal of Lymphology, 2002-2003, Vol. 10, No. 37-38, pp. 18-26,

[37] - Vokálová I. Systemic enzyme therapy in the treatment of children with recurrent infections of respiratory tract. Vox Pediatriae 2003, Vol. 2., No. 9, pp. 29 – 30.
[38] - Shved M.I., Dubkova G.I. Therapeutic efficacy of Wobenzym in patients with focal pneumonia. Visnik naukovych doslidženij 1999, No. 2, pp. 79-82.
[39] - Milus I.E. Wobenzym in the treatment of patients with psoriasis. Zurnal dermatologii i venerologii 1998, 2 (6), 35-36.
[40] - Samtsov A.V., Mazurov V. I., Tabachnov V.V. Systemic enzyme therapy in the treatment of neurodermitis (atopic dermatitis) patients. Skin and Venereal Diseases Department of Sankt-Petersburg's Military Medicine Academy Conference "New aspects of systemic enzyme therapy", Moscow, 1999.
[41] - Schved N.I., Martyniuk L.P. Clinico-laboratory evaluation of treatment efficacy in chronic pyelonephritis patients with Wobenzym. Vratschebnaya praktika 1997, 4, 38-42.
[42] - Schlüter. P. Phlogenzym® in patients with relapsing urinary tract infections: Efficacy & Tolerance. Schlüter. Gartenstraße 96, D-69502 Hemsbach, Germany. Report by: MUCOS Pharma GmbH & Co, Abt. Klinische Forschung, Kirchplatz 8, D-82538 Geretsried, Germany
[43] - Borisov O.V. Coenzyme metabolic assurance of patients with recurrent nephrolithiasis in the complex treatment by systemic enzyme therapy. Urologia 1998, 3, pp. 29-35.
[44] - Borisov A.V., Ukhal M.I., Kabak Yu.A., Borisov S.A. Immunological aspects of systemic enzyme therapy (SET) in the complex treatment of recurrent nephrolithiasis. 1st National Congress of the Ukraine on Immunology, Allergology, and Immunorehabilitation.
[45] - Stauder G., Wood G., Paczek L. Enzyme Therapy in Diabetic Nephropathy – Experimental and First Clinical Data. 6th Taormina Course of Nephrology. October 20th - 22th, 2000, pp. 227-232, Editoriale Bios 2000 PZ 22 (5-14-3)-(19-11-3).
[46] - Nouza K., Madar J. Immunomodulation in the treatment of reproduction disturbances. American Journal of Reproductive Immunology 2001, Vol. 46, No. 1, pp. 106.
[47] - Ivaniyta L.I., Ivaniyta S.O., Kornatskaya A.G., Belis N.I., Kondratiyk. Systemic enzyme therapy in the treatment of chronic salpingitis and infertility. Farm. Zh. (Kiev) 1998, No. 2, pp. 89-92.
[48] - Dittmar, F.-W. Enzyme therapy - a method of immune therapy for immunologically caused habitual abortion. Forum Immunologie 2000, No. 3/2000, II - VIII.
[49] - Friedrich, F. Wobenzym® in the Treatment of Chronic Pelvic Inflammatory Disease. Study NR.: MU-89210. Germany Report provides through: PHARMASCRIPT, Kathi Kobus increase 1, W-8190 Wolf-advice-live, to Germany Report: 30. 5. 1989.
[50] - Dittmar F.-W., Weissenbacher E. R. Therapy of adnexitis - enhancement of the basic antibiotic therapy with hydrolytic enzymes. International Journal of Experimental and Clinical Chemotherapy 1992: Vol. 5, No. 2, pp. 73-81.
[51] - Schlüter, P. Phlogenzym® in the Treatment of Chronic Prostatitis. PharmaScript, Primelweg 2, D-82538 Geretsried, Germany Date of report: October 30th, 1997.
[52] - Schlüter P. Efficacy and tolerance of oral enzyme therapy in chronic prostatitis: Results of a double-blind therapy study. European Journal for Infectious and Immunological Diseases 1998, Vol. 2, pp. 57-69.
[53] - Izbasarov A.I., Ismoldaev E.S., Khusainov T.E. Special treatment of patients suffering from a mixed copulatory dysfunction with interoreceptive syndrome. 3rd Urology Congress of Khazakhstan May 25-26, 2000., Almaty.
[54] - Loginova N.S., Naumkina N.G., Sukhikh G.T. Wobenzym in therapy of various forms of fibrocystic disease with individually selected immunomodulators. International congress "Advances in Immunology and Allergology at the Treshold of the XXI Century" May 3-6, 2000, Eilat, Israel.
[55] - Rammer E, Friedrich F. Enzyme therapy in treatment of mastopathy. A randomized double-blind clinical Study. Wien Klin Wochenschr. 1996;108(6):180-3.
[56] - F. W. Dittmarl, W. Luh. Treatment of fibrocystic mastopathy with hydrolytic enzymes. International J. of Experimental and Clinical Chemotherapie 1993: Vol. 6, No. 1, pp. 9-20 WE 13 (5-03-1) = WE 49 (5-04-1) nìm.
[57] - Kvantchakhadze R.G. Wobenzym in the complex treatment of autoimmune thyroiditis. International Journal on Immunorehabilitation, 2002, Vol. 4, No. 1, pp. 114.
[58] - Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee--a double-blind prospective randomized study. Clin Rheumatol. 2004 Oct;23(5):410-5. Epub 2004 Jul 24.
[59] - Klein G, Kullich W, Schnitker J, Schwann H. Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomised study comparing oral enzymes with non-steroidal anti-inflammatory drugs. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):25-30.
[60] - Tilwe GH, Beria S, Turakhia NH, Daftary GV, Schiess W. Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthrosis of knee joint: an open randomized controlled clinical trial. J Assoc Physicians India. 2001 Jun;49:617-21.
[61] - Guseinov N.I. Wobenzym in therapy of rheumatoid arthritis. International Journal on Immunorehabilitation 2001, Vol. 3, No. 2, pp. 73-74.
[62] - Shalamberidze L., Kartvelishvili E., Astvatsaturova T. The results of long-term use of Wobenzym in complex management of rheumatoid arthritis. International congress "Advances in Immunology and Allergology at the Treshold of the XXI Century" May 3-6, 2000, Eilat, Israel.
[63] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII,

No. 3/4, pp. 85-91.
[64] - Klein G., Kullich W. Pain Reduction in Rheumatic Diseases by Oral Therapy with Enzymes. Wien. Med. Wschr. 1999, 149, pp. 577-580.
[65] - Szilasiová A., Macejová Ž., Jautová J., Pundová L. Our experience with Wobenzym in the treatment of patients with rheumatoid and psoriatic arthritis. Prakt. Lékař 1998, Vol. 78, No. 7, pp. 366-368.
[66] - Siziakina L.P., Artemenko N.A. Clinical and immunological criteria of activity of different rheumatic arthritis courses and their treatment by Wobenzym. III. Internat. Congress on Immunorehabilitation and Rehabilitation in Medicine, Eilat, Israel, 1997.
[67] - Kovalenko V.M., Golovkov Y.Z. New possibilities of basic therapy in patients with rheumatoid arthritis on the basis of systemic enzyme therapy. Reumatologia 1998, Suppl Vol. XXXVI, Warsaw 1998, Lectures No. 212, pp 110-111.
[68] - Shaivok A.V., Movsisyan G.R., Stolyarova A.V. Wogenzym(R) in teh Treatment of Patients with Juvenile Chronic Arthritis. INt. J. Immunotherapy XIII(3/4) 93-96 (1997).
[69] - Kovalenko V.,Golovkov Y., Golovatcky I. Using of systemic enzymotherapy for treatment of rheumatoid arthritis. Rheumatologia 1998, Suppl., Vol. XXXVI, Warsaw 1998, Abst. No. 140, pp. 206.
[70] - Szilasiová A., Macejová Ž., Jautová J., Pundová L. Our experience with Wobenzym in the treatment of patients with rheumatoid and psoriatic arthritis. Prakt. Lékař 1998, Vol. 78, No. 7, pp. 366-368.
[71] - Kovalenko V.N., Golovkov Y. Z. Basic treatment of rheumatoid arthritis: new approaches. Revmatology in Europe 1997, Vol. 26, Suppl. 2, Abst. 446.
[72] - Kovalenko V.N., Siniatchenko O.V., Ignatchenko G.A., Terzov A.I., Grin V.K., Lauschkina E.M.Systemic enzyme therapy in the gout treatment. Ukrainskii kardiologitschnyi zurnal 1998: 1, 53-56.
[73] - Nouza K. Physical activity and immune system. Systemic enzyme therapy in prevention and treatment. Medicina Sportiva Boh. Slov. 1997, Vol. 6., No. 2, pp. 41 - 45.
[74] - Zuschlag J.-M. Prophylactic administration of Wobenzym to reduce consequences of sports injuries in karate fighters. MUCOS Pharma GmbH & Co, Dept. Clinical Research, Geretsried, Germany.
[75] - Kerkhoffs GM, Struijs PA, de Wit C, Rahlfs VW, Zwipp H, van Dijk CN. A double blind, randomised, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes. Br J Sports Med. 2004 Aug;38(4):431-5.
[76] - Nouza K. Physical activity and immune system. Systemic enzyme therapy in prevention and treatment. Medicina Sportiva Boh. Slov. 1997, Vol. 6., No. 2, pp. 41 – 45.
[77] - Naumenko L. Yu. Use of systemic enzyme therapy in the treatment of hand injuries and their consequences.Presented at the conference ”Current treatment aspects of wrist injuries and their consequences”, Dnepropetrovsk 1998
[78] - Vassilenko A.M., Fessenko V.I., Schvets S.V. Efficacy of systemic enzyme therapy in the treatment of patients with chronic hepatitis B. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 93-97.
[79] - Orekhov A.N., Kalenich O.S., Tertov V.V., Novikov I.D. Lipoprotein Immune Complexes As Markers of AtherosclerosisLipoprotein Immune Complexes As Markers of Atherosclerosis. Inter. Journal of Tissue Reactions 1991, Vol. XIII, No. 5, pp. 233-236.
[80] - Dzivite I., Sochnevs A., Stauder G., Zeibarts M., Lauga U.,4 Ansbergs J. Regular intake of Wobenzym® may prevent late complications in diabetes mellitus. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 143-148- ISSN 0255-9625 218 K/375 (19-05-3).
[81] - Sledzevskaya I.K., Loboda M.V., Kolesnik E.A., Babiy L.N., Fisenko L.I. Systemic enzyme treatment as a method of secondary prevention in patients after myocardial infarction in the rehabilitation period. II Mediterranean Congress of Physical Medicine and Rehabilitation, 20-23 May, 1998, Valencia, Spain. Abstracts- pp. 137 489 KA (19-08-3).
[82] - Wrba H. Systemic Enzyme Therapy - Newest Status and Progress. Therapie Woche 1987, Jahrgang 37, No. 7 SO 11 (19-02-3).
[83] - Samtsov A.V., Mazurov V. I., Tabachnov V.V. Systemic enzyme therapy in the treatment of neurodermitis (atopic dermatitis) patients. Skin and Venereal Diseases Department of Sankt-Petersburg’s Military Medicine Academy Conference "New aspects of systemic enzyme therapy", Moscow, 1999.
[84] - Sledzevskaja U. K., Šumakov V. A., Bratus V. B., Babij A., Malinovskaja U. Z., Gavrilenko T. U., Terzov A. U. Systemic enzyme therapy in the treatment of patients with myocardial infarction. Žurnal praktièeskogo vraèa 1997, No. 3, pp. 43 – 44.
[85] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp. 85-91.
[86] - Kartvelishvili E., Shalamberidze L., Torondjadze M. The results of long-term use of Wobenzym in complex management of Behcet's disease. International congress "Advances in Immunology and Allergology at the Treshold of the XXI Century" May 3-6, 2000, Eilat, Israel.
[87] - Borisov A.V., Ukhal M.I., Kabak Yu.A., Borisov S.A. Immunological aspects of systemic enzyme therapy (SET) in the complex treatment of recurrent nephrolithiasis. 1st National Congress of the Ukraine on Immunology, Allergology, and Immunorehabilitation.
[88] - Schlüter. P. Phlogenzym® in patients with relapsing urinary tract infections: Efficacy & Tolerance. Schlüter. Gartenstraße 96, D-69502 Hemsbach, Germany. Report by: MUCOS Pharma GmbH & Co, Abt. Klinische Forschung, Kirchplatz 8, D-82538 Geretsried, Germany
[89] - Dittmar F.-W., Weissenbacher E. R. Therapy of adnexitis - enhancement of the basic antibiotic therapy with hydrolytic enzymes. International Journal of Experimental and Clinical Chemotherapy 1992:

Vol. 5, No. 2, pp. 73-81.
[90] - Shaivok A.V., Movsisyan G.R., Stolyarova A.V. Wogenzym(R) in teh Treatment of Patients with Juvenile Chronic Arthritis. INt. J. Immunotherapy XIII(3/4) 93-96 (1997).
[91] - Kovalenko V.,Golovkov Y., Golovatcky I. Using of systemic enzymotherapy for treatment of rheumatoid arthritis. Rheumatologia 1998, Suppl., Vol. XXXVI, Warsaw 1998, Abst. No. 140, pp. 206.
[92] - Kovalenko V.N., Golovkov Y. Z. Basic treatment of rheumatoid arthritis: new approaches. Revmatology in Europe 1997, Vol. 26, Suppl. 2, Abst. 446.
[93] - Naumenko L. Yu. Use of systemic enzyme therapy in the treatment of hand injuries and their consequences.Presented at the conference ”Current treatment aspects of wrist injuries and their consequences”, Dnepropetrovsk 1998
[94] - Kasseroller R., Wenning H.G. Efficacy and tolerability of proteolytic enzymes as an anti-inflammatory agent in lymphoedema after axillary dissection due to mammary cancer. The European Journal of Lymphology, 2002-2003, Vol. 10, No. 37-38, pp. 18-26,
[95] - Szilasiová A., Macejová Ž., Jautová J., Pundová L. Our experience with Wobenzym in the treatment of patients with rheumatoid and psoriatic arthritis. Prakt. Lékař 1998, Vol. 78, No. 7, pp. 366-368.
[96] - Naumenko L. Yu. Use of systemic enzyme therapy in the treatment of hand injuries and their consequences.Presented at the conference ”Current treatment aspects of wrist injuries and their consequences”, Dnepropetrovsk 1998
[97] - LaMarre J, Wollenberg GK, Gonias SL, Hayes MA. Cytokine binding and clearance properties of proteinase-activated alpha 2-macroglobulins. Lab Invest. 1991 Jul;65(1):3-14.
[98] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp. 85-91.
[99] - Mazurov V.I., Stolov S.V., Linetskaya N.E., Onyschenko E.F. Systemic enzyme therapy in the complex treatment of angina pectoris. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 113-120.
[100] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp. 85-91.
[101] - Samtsov A.V., Mazurov V. I., Tabachnov V.V. Systemic enzyme therapy in the treatment of neurodermitis (atopic dermatitis) patients. Skin and Venereal Diseases Department of Sankt-Petersburg’s Military Medicine Academy Conference "New aspects of systemic enzyme therapy", Moscow, 1999.
[102] - Vokálová I. Systemic enzyme therapy in the treatment of children with recurrent infections of respiratory tract. Vox Pediatriae 2003, Vol. 2., No. 9, pp. 29 – 30.
[103] - Siziakina L.P., Artemenko N.A. Clinical and immunological criteria of activity of different rheumatic arthritis courses and their treatment by Wobenzym. III. Internat. Congress on Immunorehabilitation and Rehabilitation in Medicine, Eilat, Israel, 1997.
[104] - Wrba H. Systemic Enzyme Therapy - Newest Status and Progress. Therapie Woche 1987, Jahrgang 37, No. 7 SO 11 (19-02-3).
[105] - Dittmar F.-W., Weissenbacher E. R. Therapy of adnexitis - enhancement of the basic antibiotic therapy with hydrolytic enzymes. International Journal of Experimental and Clinical Chemotherapy 1992: Vol. 5, No. 2, pp. 73-81.
[106] - Lauer D, Reichenbach A, Birkenmeier G. Alpha 2-macroglobulin-mediated degradation of amyloid beta 1--42: a mechanism to enhance amyloid beta catabolism. Exp Neurol. 2001 Feb;167(2):385-92.
[107] - Qiu WQ, Borth W, Ye Z, Haass C, Teplow DB, Selkoe DJ. Degradation of amyloid beta-protein by a serine protease-alpha2-macroglobulin complex. J Biol Chem. 1996 Apr 5;271(14):8443-51.
[108] - Du Y, Ni B, Glinn M, Dodel RC, Bales KR, Zhang Z, Hyslop PA, Paul SM. alpha2-Macroglobulin as a beta-amyloid peptide-binding plasma protein. J Neurochem. 1997 Jul;69(1):299-305.
[109] - Hughes SR, Khorkova O, Goyal S, Knaeblein J, Heroux J, Riedel NG, Sahasrabudhe S. Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation. Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3275-80.
[110] - Mettenburg JM, Gonias SL. Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes. Protein J. 2005 Feb;24(2):89-93.
[111] - Qiu Z, Strickland DK, Hyman BT, Rebeck GW. Alpha2-macroglobulin enhances the clearance of endogenous soluble beta-amyloid peptide via low-density lipoprotein receptor-related protein in cortical neurons. J Neurochem. 1999 Oct;73(4):1393-8.
[112] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp. 85-91.
[113] - Korpan MI, Fialka V. Wobenzyme and diuretic therapy in lymphedema after breast operation. Wien Med Wochenschr. 1996;146(4):67-72; discussion 74.
[114] - Schlüter, P. Phlogenzym® in the Treatment of Chronic Prostatitis. PharmaScript, Primelweg 2, D-82538 Geretsried, Germany Date of report: October 30th, 1997.
[115] - Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee--a double-blind prospective randomized study. Clin Rheumatol. 2004 Oct;23(5):410-5. Epub 2004 Jul 24.
[116] - Mazourov V.I., Lila A.M., Klimko N.N., Raimuev K.V, Makulova T.G. The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis. Inter. Journal of Immunotherapy 1997, Vol. XIII,

No. 3/4, pp. 85-91.