2017 Edition of eBook

Systemic Enzyme Therapy

My Experience with the Wobenzym® Formulations

by Dr Joseph J Collins, RN, ND

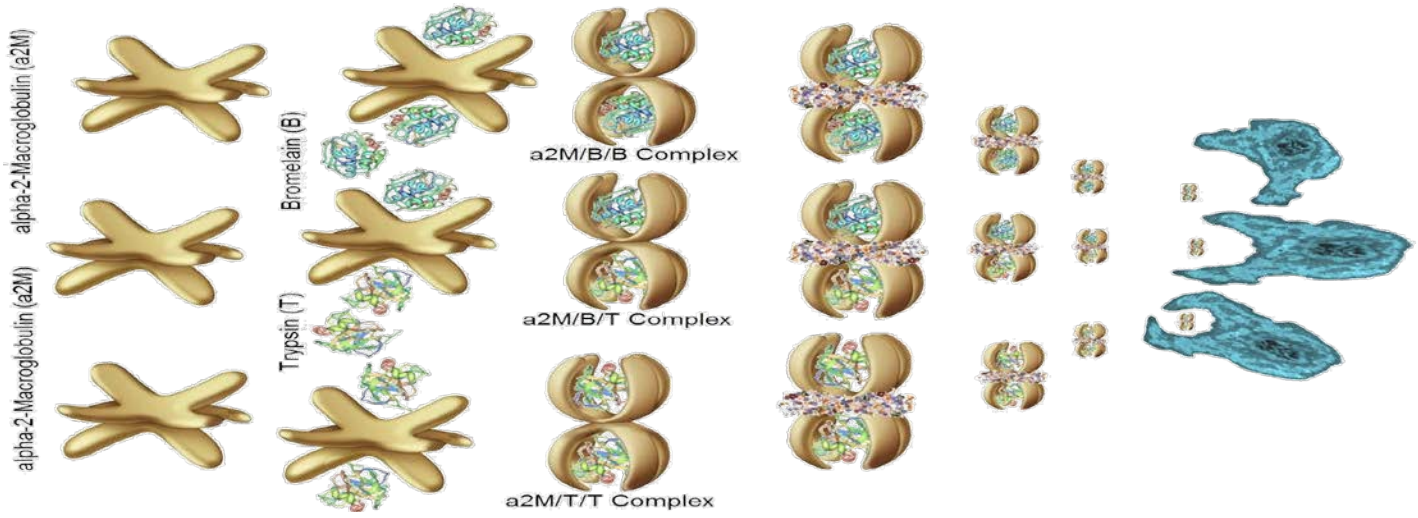
Clinical & Personal Experiences with Wobenzym® Formulations
Clinical Efficacy of Systemic Enzyme Support
How Systemic Therapy Works Throughout the Body
Exhaustive Review of International Literature.
How Systemic Therapy Works (with illustrations)
Research on Dozens of Conditions:

Alzheimers
Angina
Atherosclerosis
Autoimmune Thyroid Disease
Behçets
Diabetes
Diabetic Nephropathy
Eczema
Fibrocystic Breast
Glomerulonephritis
Gout
Hepatitis
Infertility & Miscarraiges
Kidney Stones
Lymphedema
Multiple Sclerosis
Myocardial Infarction
Osteoarthritis
Pelvic Inflammatory Disease
Prostatitis & Copulatory DyFxn
Psoriasis
Pyelonephritis
Respiratory Tract Infections
Rheumatoid Arthritis
Sports Medicine
Tendonitis
Thrombophlebitis
Urinary Tract Infections
Uveitis

Dosage Guidelines for:

- **Wobenzym® N**
- **Wobenzym® PS**
- **Wobenzym® Plus**

Frequently Asked Questions (FAQs)
References



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I first started using Wobenzym® formulations in the early 1990s. Beginning in 2008 I started to compile the international literature on Wobenzym® formulations. This compilation has been used by clinicians, writers and researchers interested the properties of the formulations. The information has been posted on a website, as well as two educational posters and a number of PowerPoint presentations. The compilation has been updated, edited, and converted to this book (eBook).

This 2017 version of the ebook has a completely updated section on the Dosage Guidelines for the various Wobenzym® formulations, which now includes the dosage guidelines for Wobenzym® Plus. The information on dosages for Wobenzym® Plus is based on published dosages for Wobenzym® PS. The dosage has been modified to reflect that two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets. As such, Wobenzym® PS dosages of six (6) tablets have been changed to Wobenzym® Plus dosage of four (4) tablets.

Considerable editing and updating of the original works has taken place when converting the collective works into this ebook. The work has been updated to mention specific disease states, which were only refered to in general terms in the published posters.
For example, in the first poster the sentence says: "Promotes endogenous degradation and clearance of the amyloid beta (Aβ) peptide, and could support healthy neurological aging.[7-12]", whereas in this book the specific formulation and the specific disease is mentioned, so the statement now reads: "**Wobenzym® N** promotes degradation and clearance of the amyloid beta (Aβ) peptide, and could probably reduce the risk of developing **Alzheimer's Disease**.[7-12]"

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CLINICAL & PERSONAL EXPERIENCES WITH WOBENZYM® FORMULATIONS

Clinical Experiences, my Wobenzym® Testimony, & Why I Started my Research into Wobenzym®
Dr. Joseph J Collins, RN, ND

As a Naturopathic Physician I have found that systemic enzyme support is a valuable treatment modality both in and of itself, and as an adjuvant for nutritional, herbal, homeopathic, hormonal, and other therapies.
I use the term "systemic enzyme support" because after reviewing all the science involved, I realize that the Wobenzym® formulations support immune processes that naturally occur in the human body. As such, the Wobenzym® formulations enhance the ability of the body to protect itself the way it was designs. Sometimes I use the term "systemic enzyme therapy", but given the fact that we are supporting an endogfenous system, I tend to use the word "support" more often.
The systemic enzyme formulation that first got my attention was the formulation designed by Professor Max Wolf and biochemist Helene Benitez. Working together, Wolf and Benitez carried out thousands of tests to isolate and purify proteolytic enzymes out of animal and plant organisms. They researched various enzyme combinations and added these mixtures to cell cultures, such as cancer cells. Over the course of years, they were able to continuously refine the enzyme compounds. The optimal combination that helped treat inflammatory diseases and degenerative diseases was first named "Wolf-Benitez-Enzyme", which was later abbreviated to "Wobenzym®". The Wobenzym® formulation was universally found to be quite effective, and was subsequently validated by many international research papers validated. For many years, my experience with systemic enzyme support was very positive, with impressive results.
Unfortunately, over the years I found myself trying some of the "new" enzyme formulations on the market. In an effort to be fair and objective, I gave the "new" enzymes a chance. My trust in systemic enzyme support quickly faded. I found those "new enzymes" did not have the profound therapeutic effect that I had observed with Wobenzym®. Ultimately, I found myself rarely using enzymes in my practice due to the relative ineffectiveness of the "new" enzymes. Later, I realized that many of these "new" enzyme formulations actually used research that was published on Wobenzym®. Some went as far as to remove the word "Wobenzym®" from the title of the research, or from abstracts of the research. Their "new" formulations were not Wobenzym®.
The 2003 research on Wobenzym® for the treatment of lymphedema (and a review of actual Woebnzym® research) renewed my awareness of the unique benefits of Wobenzym®. With Wobenzym® I found the means to effectively treat a difficult case of lymphedema, as well as resistant cases of chronic inflammation, including rheumatoid arthritis. In addition, I found that it dramatically helped with acute inflammation such as sports trauma.
Also important, I noted that other therapies that I used - nutritional, herbal, homeopathic and hormonal – are much more effective when Wobenzym® is used as an adjuvant. An adjuvant is a substance that increases the effectiveness of other therapies. This made sense, since research shows Wobenzym® increases the effectiveness of antibiotics and other drugs. I now know that Wobenzym® helps clean up intracellular debris and improve cell signaling, so the increased efficacy of other therapies is understandable.
What impresses me most about Wobenzym® is not just my own experiences using it, but the experience of medical researchers and writers from around the world. I used hundreds of those references to create the two systemic enzyme support medical eduction posters that have been converted into this book. In most cases, the complete abstracts or reseach research summaries of those references are contained in this book.
Wobenzym® research continues. In February of 2014, a study involving 160 healhty marathon runners concluded; "that marathon-induced inflammatory perturbations and the incidence of subsequent URTI, muscular damage, and changes of hemostasis can be positively influenced by the anti-edematous, anti-inflammatory, antioxidant, and fibrinolytic effects of oral hydrolytic enzymes and flavonoids (Wobenzym)." As research continues, and new clinical insights become evidenced, this eBook will be updated periodically.

Stay well,
Dr Joseph J Collins, RN, ND

Other Testimonies of Personal Experiences with Wobenzym®

In addition to my experiences with Wobenzym® formulations, I have received a number of testimonies through the years. I wanted to share a few of those testimonies. I am only sharing a few because to share them all would take too much space. In fact, I quit asking for testimonies because there were so many, that it required a large portion of my time to respond to. For those of you who have testimonies you want to share, I suggest you share them with yoru friends and families, so the people you area bout can experience the same benefits you have recived from taking Wobenzym®.

Improved Recovery from Surgery, Better Digestion and Skin Health

I started taking Wobenzym® after a surgery to remove nine screws and two metal plates that had been placed in my ankle and foot over eight years ago after a traumatic fall. My recovery was much quicker than expected. I also found that my new scars have disappeared and the old ones have faded.

My life long struggle with IBS and eczema has traumatically improved. My stomach blotting has decreased and my skin is much healthier.

A.C., Cedar Rapids, IA

Frozen & Painful Tennis/Golf Elbow Improved

I suffered from tennis/golf elbow for the past two years. My arm remained permanently bent at a 15-degree angle and would not straighten out. I wore a brace, had physical therapy, and took steroid shots of cortisone to alleviate the pain and try to straighten my arm out. Nothing worked. My golf game suffered terribly as a result of this condition. I started taking Wobenzym® N 6 months ago on a regular basis to see if it would make a difference. I am now 98% pain free and my arm has straightened out almost completely! I can hardly wait to get back on the links this spring!

A.M.W., Pittsburgh, PA

Ironman World Championship Athlete Shortens Recovery Time

I am an avid tri-athlete training for the 2009 Ironman World Championship. I rely on Wobenzym® daily to help me recover from training sessions and races. I have found after taking Wobenzym® that my recovery time is shortened and delayed onset muscle soreness is rarely an issue after difficult training sessions. I make a point to take tablets first thing in the morning before my workouts and immediately afterwards.

T.J.M, Houston, TX

Gout Attack Subsides Quickly – Able to Lose Weight Now

My brother had a severe gout attack. He was started on a therapeutic dosage (15 tablets a day for 1 month), but within six hours of starting Wobenzym® N his flare up subsided. He stayed on the Wobenzym® N and has lost 22 pounds so far.

D.B., Aventura, FL

Severe Arthritis Pain of Recent Onset Fully Resolved, Daily Workout, Including Boxing, Resumed

My husband, 33 years old, recently started to have severe pain in his right wrist. He met with his PCP to evaluate the problem, as he thought it was a stress fracture or worse. He was told that he was experiencing the onset of Arthritis and there was little that he could do for it other than prescription medication. He started using Wobenzym® N and said that he would "give it a shot" before filling his prescription from his Doc. Within 3 days of using Wobenzym® N he was able to get back into his daily workouts with no pain. He was able to do push-ups, pull downs, box, and lift our children with no tightness or shooting pain. Wobenzym® has allowed him to remain off prescription medications and maintain his normal routine.

S.A., Sewickley, PA

Shoulder Pain and Back Pain Improved
Overall Health & Anti-Aging Benefits Appreciated
Wobenzym® is a terrific supplement for inflammation. I engage in a very athletic lifestyle which can easily contribute to aches, pains and discomfort. This is compounded by a reverse curvature in my neck that causes painful shoulder and back pain. Since taking Wobenzym®, I feel a huge difference in the frequency of discomfort associated with my activities & limitations. I also take this supplement for overall health and the anti-aging benefits.
D.K., San Ramon, CA

Rheumatoid Arthritis of Over 30 Years Now Improved
I suffer from rheumatoid arthritis, which has been an aggressive form I've lived with for over 30 years. My medications mask some of the discomfort, but not much. My doctors have told me to go home and that there is nothing more that they can do for me. My daughter got me started on Wobenzym® and I have noticed improvement in the severity of flare-ups and other types of discomforts. It is a terrific product that I would highly recommend to anyone suffering from joint issues like mine.
L.K., Cleveland, OH

Painful & Swollen Sprain Dramatically Improved
I rolled my foot pretty badly while running resulting in a painful and swollen sprain, unable to support my weight. I was sure I would be off of it for an extended period of time. I immediately began taking Wobenzym® in high doses along with wrapping and icing the foot. Much to my surprise the sprain was so improved three days later that I was able to walk a three-mile loop, and I was back to running the day after that. It really works!
L.A.F., Seattle, WA

Tennis Elbow Greatly Improved in Two Weeks
I suffered from tennis elbow in my left arm last year, and after ten months of taking 4 tablets of [naproxen]* per day, and one month of wearing a wrist brace, my pain finally went away. This fall, I got tennis elbow in my right arm, and I heard about the positive effects Wobenzym® might have for this condition. Tennis elbow is basically tendonitis, or inflammation of tendons in the arm, and I was told that Wobenzym® would help relieve this inflammation. After only two weeks of taking 6 Wobenzym® tablets per day, my condition has greatly improved, and I am playing tennis again. I was amazed at how quickly they worked, with no side effects whatsoever. It's great to actually feel the benefits of a supplement, since vitamins, etc. are beneficial, but those benefits can sometimes be hard to quantify. I would strongly recommend Wobenzym® to anyone with similar pain or inflammatory issues. *[trade name was replaced with generic name]
D.L., Annandale, VA

Improved recovery from Sinus Surgery
I recently had oral surgery that involved a bone graft, sinus lift, and implant. The surgeon noted that my recovery would be a bit longer than I expected, but he wanted to see me in a week's time to be sure that I was healing correctly. As soon as the bleeding stopped, I took Wobenzym® twice a day to help with the inflammation that I experienced post surgery. The following week I went into the surgeon's office, and he was astounded at how well I was recovering. He asked how many pain killers I was taking, and was shocked when I said I did not need them after the bleeding stopped. Wobenzym® relieved the pain, and improved my recovery process.
E.A.W., Duluth, GA

Tumors are Shrinking & White Lumps in Lips Gone
I found this site on the internet when a friend down the road was diagnosed with Stage 4 Cancer. He's a farmer & had no idea he was in this much trouble. All he knew was that he couldn't sleep at night and his whole body was aching. He came to us & told us the Hospital gave him 4 months to live and that he was a stage 4, so he would die of Cancer. He said he actually threw up on the way home after they told him the news. Then they were supposed to operate on his larger tumors near his bowels first, opened him up & then never took any tumors out, just closed him up.
Well, we ordered this Wobenzym® N for him & the Apricot Kernels to take with it. He has taken this stuff religiously now for 4 months & he actually has an appetite, gained weight & he was told yesterday that his tumors are shrinking and they don't know why.

My son had these white lumps on the inside of his lips and he was here from SC for a week -2 weeks ago, & he has been taking the pills & he said the lumps are gone. So we totally believe in your Wobenzym® N.
I'll keep you updated on the Farmer story if you like.....Thanks for giving this young man a will to survive, he is totally dedicated to what he is taking & I hope he beats this cancer.....
K.V.N., Ontario, New York

Gout, Plantar Fasciitis & Heal Spur Relief Started on Fifth Day
The reason for this communication, and in particular, this subject, concerning WOBENZYM® N, is to make you aware of my experience using the product WOBENZYM® N
My health issues include Gout, Plantar Fasciitis and Heal Spurs.
For any individuals who have these issues, or just one of them, my sympathies are extended for I realize how their quality of life can deteriorate in very short order. In my case I have all three along with Arthritic aggravations in several areas.
In my life, I require extensive standing and walking, therefore you can appreciate how this lifestyle can be extremely painful while enduring these issues. Standing and walking for long periods is overbearing at the best of times. My personal endeavors' are limited and this situation certainly makes me feel, at the best of times, inadequate.
After communicating, with one of your Professional Advisors, I was, and I have to admit, extremely reluctant to get my hopes up about any product that could possibly help with my situation.
Most certainly, other issues were the inability to use products that focus on my ailments but I could not consume due to conflicts with current medication.
Needless to say, I began using your product as directed. Three to four days into my trial, I was constantly looking for indicators even though I was not sure what to expect. I was considering stopping the regiment.
On day number FIVE, I awoke and proceeded to go about my morning duties when excitedly I realized I was not limping with regularity as I had been for such a long time previous to taking WOBENZYM® N.
Most of all, even though I felt a little discomfort, the major aggravation seemed to lessen noticeably as the days went by from there on.
In addition, my energy level began to spring back to life. My state of mind changed to a more positive mode. I noticed that as more days went by I was able to focus on more meaningful directions in life rather than the pain I was enduring.
It seems that this product also is relieving pain I would experience in my hips and knees when I was overdoing my workload a little. My body is not haunting me in many of the ways it would prior to experiencing WOBENZYM® N.
Thank you for recognizing my dilemma and taking an interest in my health issues. Most of all, THANK YOU for introducing me to a product that has given me the ability to return to the active life style I enjoy so much.
R.J.S., Ontario, Canada

Clinical Efficacy of Systemic Enzyme Support

Dr Joseph J Collins, RN, ND - 2009, Updated 2016

Clinical observations and literature review both affirm the conviction that systemic enzyme support with Wobenzym® N, Wobenzym® PS or Wobenzym® Plus 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, Wobenzym® PS or Wobenzym® Plus - 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. MUCOS Pharma, Wobenzym® N, Wobenzym® PS and Wobenzym® Plus are still manufactured in Germany, but is distributed by 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, Wobenzym® PS and Wobenzym® Plus enteric coated, formulation 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, Wobenzym® PS or Wobenzym® Plus 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 a 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 clinical-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, Wobenzym® PS or Wobenzym® Plus, 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, Wobenzym® PS and Wobenzym® Plus are manufacture by that same company, and available throughout the United States. Clinical observations and literature review both affirm the conviction that Wobenzym® N, Wobenzym® PS and Wobenzym® Plus are an essential component for successful management of inflammation disorders and other conditions with immune system dysregulation due to its high degree of clinical efficacy.

See References for "Clinical Efficacy of Systemic Enzyme Support" in Reference section at end of book.

HOW SYSTEMIC ENZYME THERAPY WORKS

This section of the book is derived from educational posters written in 2008 and 2009. The first poster focused on research done with the **Wobenzym® N** formulation. **Wobenzym® N** contains specific enzymes including trypsin, chymotrypsin, bromelain, papain, and pancreatin (containing additional endoproteinases as well as exopeptidases, α-amylase and lipase), as well as rutosid, a bioflavonoid. The second poster focused on research done on the enzyme formulation that is used in **Wobenzym® PS** and **Wobenzym® Plus**. The ingredients of **Wobenzym® PS** and **Wobenzym® Plus** are the same. They are higher dosages of bromelain, trypsin and rutoside. Due to the extreme popularity of **Wobenzym® PS**, which has a recommended dosage of three tablets twice a day, it has been upgraded to Wobenzym® Plus, which only requires two tablets twice a day.

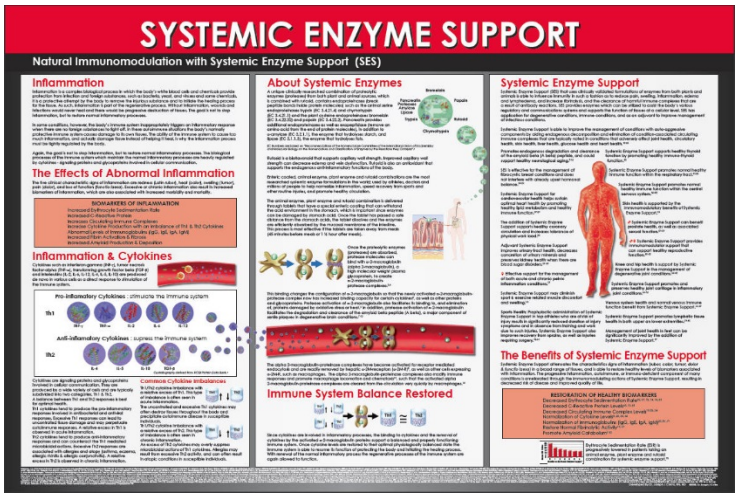
Considerable editing and updating of the original works has taken place when converting the collective works into this book. The work has been updated to mention specific disease states, which were only refered to in general terms in the published posters. For example, in the first poster the sentence says: "Promotes endogenous degradation and clearance of the amyloid beta (Aβ) peptide, and could support healthy neurological aging.7-12", whereas in this book the specific disease is mentioned, so the statement now reads: "**Wobenzym® N** promotes degradation and clearance of the amyloid beta (Aβ) peptide, and "could probably reduce the risk of developing **Alzheimer's Disease**.[7-12] "

Wobenzym® N

(with illustrations)

(**Content originally published as a poster**: Systemic Enzyme Support: Natural Immunomodulation with Systemic Enzyme Support Poster © 2008-2016 Dr. Joseph J Collins, RN, ND. All rights Reserved)

Last Reviewed 2016.



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To download documents please visit: **www.YourHormones.com/documents**

As noted under the heading "HOW SYSTEMIC ENZYME THERAPY WORKS", **Wobenzym® N** contains specific enzymes including trypsin, chymotrypsin, bromelain, papain, and pancreatin (containing additional endoproteinases as well as exopeptidases, α-amylase and lipase), as well as rutosid, a bioflavonoid.

References for the reference numbers in this specific section are listed in the end of the book under "Systemic Enzyme Support: Natural Immunomodulation with Systemic Enzyme Support Poster"

The clinical references are specificly on research done with **Wobenzym® N**.

Systemic Enzyme Support

Natural Immunomodulation with Systemic Enzyme Support

By Dr Joseph J Collins, RN, ND

Inflammation

Inflammation is a complex biological process in which the body's white blood cells and chemicals provide protection from infection and foreign substances, such as bacteria and viruses and some chemicals. It is a protective attempt by the body to remove the injurious substance and to initiate the healing process for the tissue. As such, inflammation is part of the regenerative process. Without inflammation, wounds and infections would never heal and there would be progressive destruction of tissues. The goal is not to stop inflammation, but to restore normal inflammatory processes.

In some conditions, however, the body's immune system inappropriately triggers an inflammatory response when there are no foreign substances to fight off. In these autoimmune situations the body's normally protective immune system causes damage to its own tissues. The ability of the immune system to cause too much inflammation, and actually damage tissue instead of helping it heal, is why the inflammation process must be tightly regulated by the body.

Again, the goal is not to stop inflammation, but to restore normal inflammatory processes. The biological processes of the immune system which maintain the normal inflammatory processes are heavily regulated by cytokines - signaling proteins and glycoproteins involved in cellular communication.

The Effects of Abnormal Inflammation

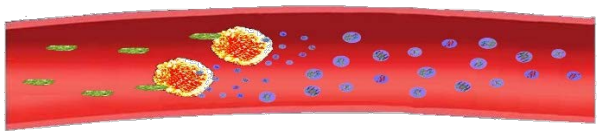
The five clinical characteristic signs of inflammation are **redness** (Latin *rubor*), **heat** (*calor*), **swelling** (*tumor*), **pain** (*dolor*), and **loss of function** (*functio laesa)*. Excessive or chronic inflammation also result in increased biomarkers of inflammation, which are also associated with increased morbidity and mortality.

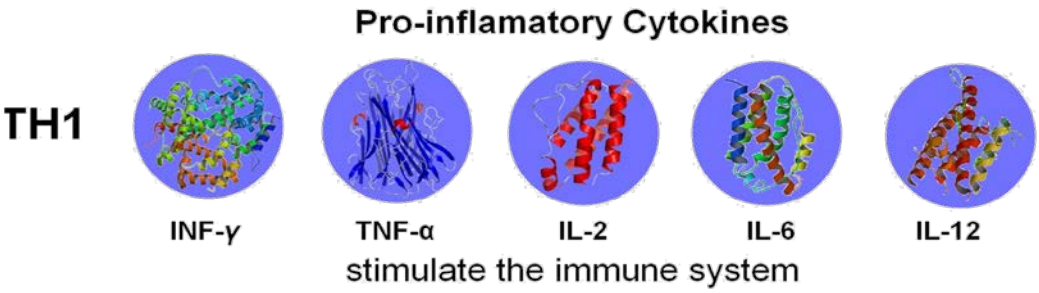
BIOMARKERS OF INFLAMMATION

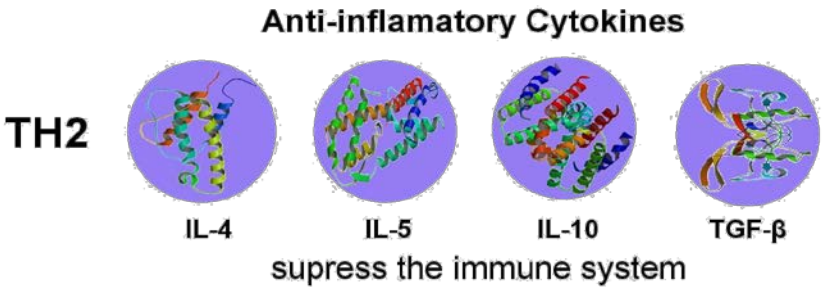
Increased Erythrocyte Sedimentation Rate
Increased C-Reactive Protein
Increases Circulating Immune Complexes
Increase Cytokine Production with an Imbalance of Th1 & Th2 Cytokines
Abnormal Levels of Immunoglobulins (IgG, IgE, IgA, IgM)
Increased Fibrin Activation & Fibrosis
Increased Amyloid Production & Deposition

Inflammation & Cytokines

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 in various cells as a direct response to stimulation of the immune system.





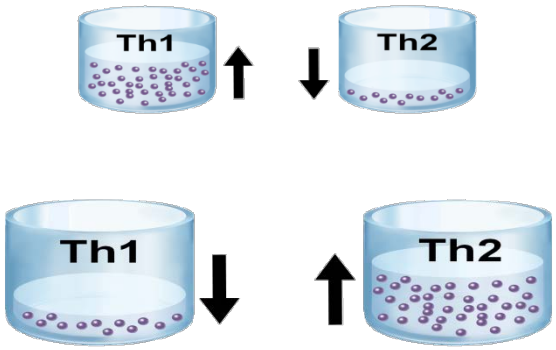


Crystallography images are derived from RCSB Protein Data Bank. [1]

Cytokines are signaling proteins and glycoproteins involved in cellular communication. They are produced by a wide variety of and are typically subdivided into two categories, Th1 & Th2. A balanced between Th1 and Th2 responses is best for optimal health.
Th1 cytokines tend to produce the pro-inflammatory responses involved in antibacterial and antiviral responses. Excessive Th1 responses can lead to uncontrolled tissue damage and may perpetuate autoimmune responses. A relative excess in Th1 is 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 observed in chronic inflammation.

Common Cytokine Imbalances

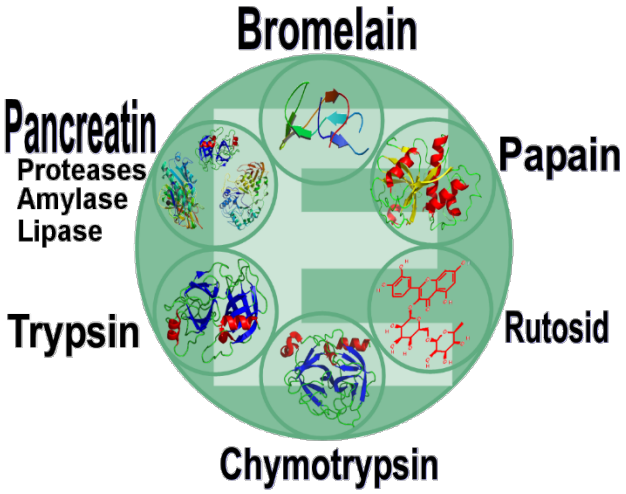
Th1/Th2 cytokine imbalance with a relative excess of Th1. This type of imbalance is often seen in acute inflammation. The uncontrolled and excessive Th1 cytokines may often destroy tissues throughout the body and precipitate autoimmune disease in susceptible individuals.
Th1/Th2 cytokine imbalance with a relative excess of Th2. This type of imbalance is often seen in chronic inflammation. An excess of Th2 cytokines may overly suppress microbicidal actions of Th1 cytokines. Allergies may result from excessive Th2 activity, and can often result in atopic conditions in susceptible individuals.



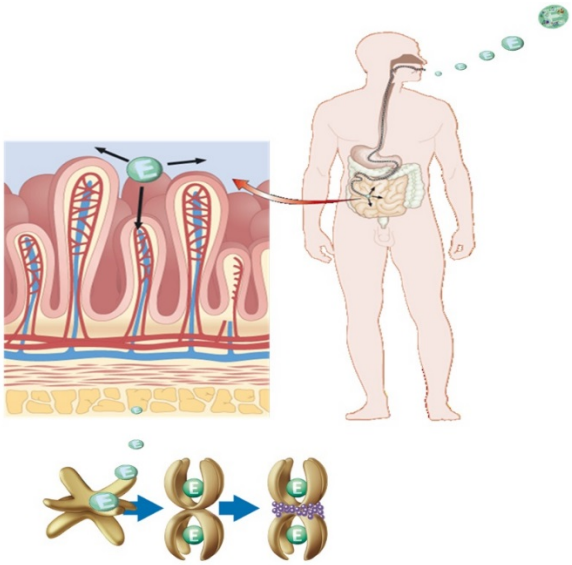
About Systemic Enzymes

A unique clinically researched combination of proteolytic enzymes (proteases) from both plant and animal sources, which is combined with rutosid, contains endoproteinases (break peptide bonds inside protein molecule) such as the animal serine endoproteinases trypsin (EC 3.4.21.4) and chymotrypsin (EC 3.4.21.1) and the plant cysteine endoproteinases bromelain (EC 3.4.22.32) and papain (EC 3.4.22.2). Pancreatin provides additional endoproteinases as well as exopeptidases (remove an amino acid from the end of protein molecule), in addition to α-amylase (EC 3.2.1.1), the enzyme that hydrolyses starch, and lipase (EC 3.1.1.3), the enzyme that hydrolyses fats.

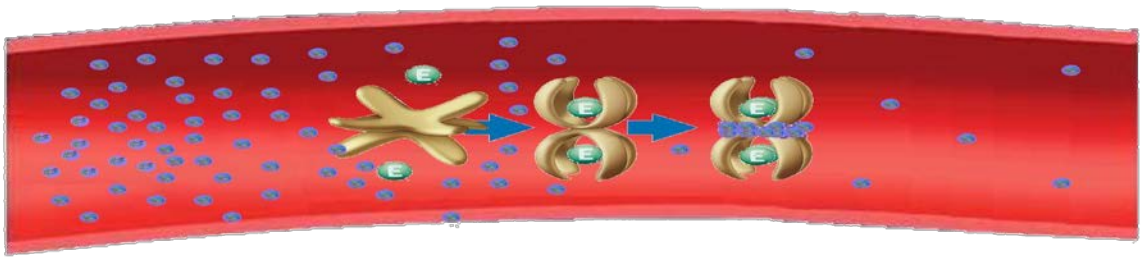
EC Numbers are based on "Recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the Nomenclature and Classification of Enzymes by the Reactions they Catalyse".[2]



Rutosid is a bioflavonoid that supports to capillary wall strength. Improved capillary wall strength can decrease edema and vein dysfunction. Rutosid is also an antioxidant that supports the endogenous anti-inflammatory functions of the body.
Enteric coated, animal enzyme, plant enzyme and rutosid combinations are the most researched systemic enzyme formulations in the world; used by athletes, doctors and millions of people to help normalize inflammation, speed recovery from sports and other routine injuries, and promote healthy circulation.

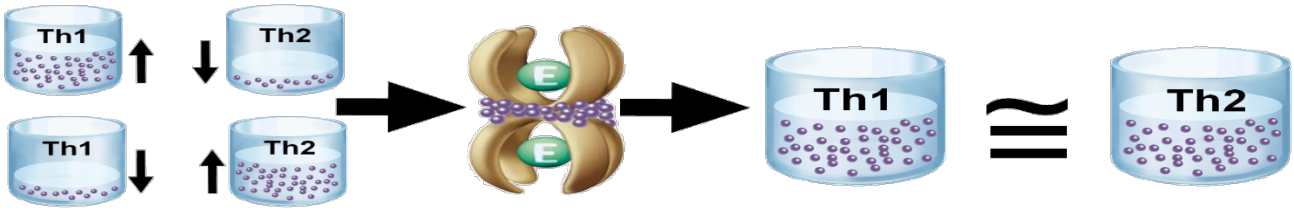


The animal enzyme, plant enzyme and rutosid combination is delivered through tablets that have a special enteric coating which can withstand the acid environment in the stomach, which is important since enzymes can be damaged by stomach acid. Once the tablet has passed a safe distance from the stomach 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 (45 minutes before meals or 1 ½ hour after meals).
Once the proteolytic enzymes (proteases) are absorbed, two protease molecules can bind with each α-2-macroglobulin (alpha 2-macroglobulin), a high molecular weight plasma glycoprotein, to create α-2-macroglobulin-protease complexes.[3,4]
This binding changes the configuration of α-2-macroglobulin so that the newly activated α-2-macroglobulin-protease complex now has increased binding capacity for certain cytokines[5], 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.[6] Protease activation of α-2-macroglobulin also facilitates the degradation and clearance of the amyloid beta peptide (A beta), a major component of senile plaques in Alzheimer's patients.[7-12]



The alpha 2-macroglobulin-proteinase complexes have become activated for receptor mediated endocytosis and are readily removed by hepatic α-2M-receptors (α-2M-R)[5], as well as other cells expressing α-2M-R, such as macrophages. The alpha 2-macroglobulin-proteinase complexes also modify immune responses and promote macrophage locomotion and chemotaxis[13], such that the activated alpha 2-macroglobulin-proteinase complexes are cleared from the circulation very quickly by macrophages[14].

Immune System Balance Restored



Since cytokines are involved in 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. 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.

Systemic Enzyme Support

Systemic Enzyme Support which uses 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. SET 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. SET has application for degenerative diseases, autoimmune diseases, and as an adjuvant to improve efficacy of anti-infectives in infectious diseases.
Improving the treatment of conditions with an auto-aggressive **Wobenzym® N** (also called **"**Systemic Enzyme Therapy" (SET) promotes the decomposition and elimination of disease associated circulating immune complexes, thereby component such as **rheumatoid arthritis**, **atherosclerosis**, **atopic dermatitis**, **Behçet's disease**, **chronic hepatitis**, **diabetes mellitus**, and **myocardial infarction**.[15-23]

Wobenzym® N has been used in various conditions, such as:

Wobenzym® N promotes degradation and clearance of the amyloid beta (Aβ) peptide, and "could probably reduce the risk of developing **Alzheimer's Disease**.[7-12]

- **Wobenzym® N** is an effective therapy for the management of **fibrocystic breast disease** and does not interfere with already upset hormonal balance.[24-26]
- **Wobenzym® N** adjuvant in **myocardial infarction** reduces risks of re-infarction due to hypolipidemic and immunonormalizing benefits.[27-29]
- The addition of **Wobenzym® N** reduces frequency and intensity of **angina pectoris** attacks and increased tolerance of physical work load.[30]
- Adjuvant **Wobenzym® N** improves relapsing **UTI**s **pyelonephritis** recovery and decreases recurrence of **kidney stones** and progression of **diabetic nephropathy**.[31-35]
- Effective treatment when using **Wobenzym® N** in chronic **pelvic inflammatory disease (PID**) and as adjuvant in treatment of acute **adnexitis**.[36,37]
- **Sport & exercise related muscle pain & inflammation** are decreased with "excellent results" when using **Wobenzym® N**.[38]
- **Wobenzym® N** is highly effective resolution of **lymphedema** in both upper and lower extremities due to fibrinolytic & antiedematous effects.[39-45]
- Disease of venous system, including acute **thrombophlebitis** and **postthrombophlebitic syndrome**[46-49] are improved when **Wobenzym® N** is used.
- **Sports Medicine**: Prophylactic administration of **Wobenzym® N** 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. **Wobenzym® N** also **improves recovery from sprains, as well as injuries requiring surgery**.[78-81]
- **Wobenzym® N** treatment of **autoimmune thyroid disease** resulted in significant decrease of TSH, anti-TG & anti-TPO and allowed lowering of L-thyroxine dose.[50]
- **Wobenzym® N** resulted in reduction of both frequency and severity of recurrent **respiratory tract infections**.[51,52]

- **Wobenzym® N** decreased the number and duration of **multiple sclerosis** attacks due to a decrease in inflammatory activity.[53-55]
- Inclusion of **Wobenzym® N** in treatment of **psoriasis** significantly decreases the exsudative component of exacerbation, increased regression and decreases recurrence.[56]
- **Wobenzym® N** is an efficient therapy for both bacterial and abacterial **prostatitis**, as well as associated **sexual dysfunction**.[57-59]
- **Wobenzym® N** is an effective immunomodulator for both autoimmune & alloimmune **infertility**.[60-62]
- **Wobenzym® N** is an effective and safe alternative to NSAIDS in the treatment of painful episodes of **osteoarthritis** of the knee and hip.[63-65]
- **Wobenzym® N** protects and preserves joint cartilage significantly better than NSAIDs in **rheumatoid arthritis**.[66-76]
- **Gout** therapies are significantly improved by the addition of **Wobenzym® N**.[77]

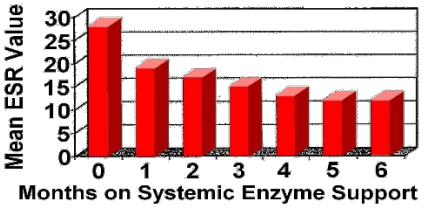
The Benefits of Systemic Enzyme Support

Systemic Enzyme Support attenuate the characteristics signs of inflammation in a broad range of tissues (*rubor, calor, tumor, dolor & functio laesa*), and are able to restore healthy levels of biomarkers associated with inflammation. The progressive inflammation, autoimmune, or immunodeficient component of many conditions is ameliorated through the immunomodulating actions of *systemic enzyme support*, resulting decreased risk of disease and improved quality of life.

RESTORE HEALTHY BIOMARKERS

Decreased Erythrocyte Sedimentation Rate[32,37,73,74,76,81]
Decreased C-Reactive Protein Levels[45,70,81]
Decreased Circulating Immune Complex Levels[15-23,34]
Normalization & Rebalance of Th1 & Th2 Cytokine Levels[5,22,30,68]
Normalization of Immunoglobulins (IgG, IgE, IgA, IgM)[20,51,71]
Restore Normal Fibrinolytic Activity[19,30,47]
Promote Amyloid Catabolism[7-12]

Erythrocyte Sedimentation Rate (ESR) was progressively lowered in patients taking an animal enzyme, plant enzyme and rutosid combination for *systemic enzyme support*.[73]



References:

References for the reference numbers in this preceding section are listed in the **References** section at end of the book under "**Systemic Enzyme Support: Natural Immunomodulation with Systemic Enzyme Support Poster**"

Wobenzym® PS & Wobenzym® Plus

(with illustrations)

(**Content originally published as a poster:** PROFESSIONAL SYSTEMIC ENZYME SUPPORT: Advanced Immunomodulation with Professional Strength Systemic Enzyme Support © 2009 – 2016 Dr. Joseph J Collins, RN, ND. All rights Reserved)
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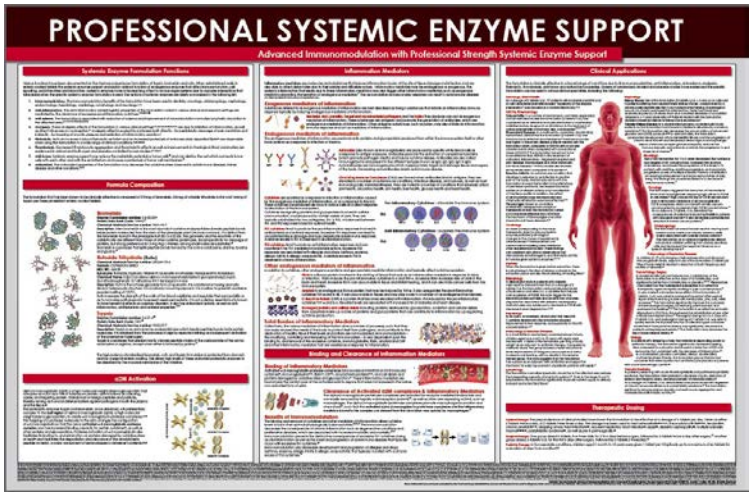

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Display this poster at your clinic or other place of business to show your patients and customers that you have studied and are knowledgable in the specialty of managing systemic inflammation and other immune disorders.

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As noted under the heading "HOW SYSTEMIC ENZYME THERAPY WORKS", the specific ingredients of **Wobenzym® PS** and **Wobenzym® Plus** are the same. They are higher dosages of bromelain, trypsin and rutoside. Due to the extreme popularity of **Wobenzym® PS**, which has a recommended dosage of three tablets twice a day, it has been upgraded to **Wobenzym® Plus**, which only requires two tablets twice a day.

References for the reference numbers in this specific section are listed in the end of the book under "PROFESSIONAL SYSTEMIC ENZYME SUPPORT: Advanced Immunomodulation with Professional Strength Systemic Enzyme Support Poster".
The clinical references are specificly on research done with the formulation used in **Wobenzym® PS** and **Wobenzym® Plus**. Wobenzym® PS is known as Phlogenzym in Germany and other countries.

PROFESSIONAL SYSTEMIC ENZYME SUPPORT

Advanced Immunomodulation with Professional Strength Systemic Enzyme Support

By Dr Joseph J Collins, RN, ND

Systemic Enzyme Formulation Functions

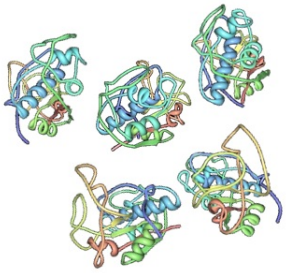
Various functions have been documented on the German polyenzyme formulation of trypsin, bromelain and rutin. When administered orally in enteric coated tablets the systemic enzymes support and sustain optimal function of endogenous enzymes that affect immune function, cell signaling, oxidative stress and blood flow. Systemic enzymes have a far-reaching affect in various organ systems due to complex interactions that take place when the specific systemic enzyme formulation is used. The actions of systemic enzymes are briefly summarized in the following list:

1. **Immunomodulatory.** The imunomodulatory benefits of the formulation have been used in dentistry, oncology, otolaryngology, nephrology, endocrinology, hepatology, cardiology, lymphology and neurology. [1-16]
2. **Anti-inflammatory.** The anti-inflammatory (antiphlogistic) properties of the formulation noted in various clinical and research settings are mediated by the clearance of excessive pro-inflammatory cytokines. [7,12,15,17-33]

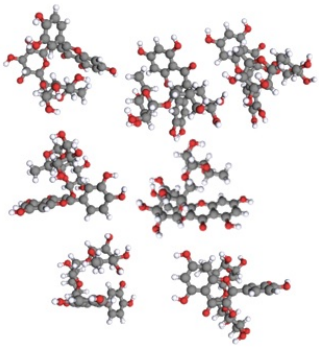
3. **Anti-edema.** The formulation is associated with reduction of edema and improvement of microcirculation normalize lymphatic circulation in the affected area. [5,7,12-15,18,19,22,25,26,34-36]
4. **Analgesic.** The analgesic effects of the formulation in various clinical settings [7,15,18,22,27,29,33,34,37,38] are due to inhibition of inflammation, as well as direct influences on nociceptors. [19] Analgesic effect is evoked by protease peptidolytic cleavage of pain mediators, by protease lowering of oncotic pressure, and by restriction of control of inflammatory reaction. [5]
5. **Fibrinolytic.** Both an increase in blood fibrinolytic activity [39] and an increased proteolysis of extravascularly deposited fibrin [23] are observable when using the formulation in a wide range of clinical conditions. [7,12-14,37,40]
6. **Thrombolysis.** Decreased thrombocyte aggregation and thrombolytic effects as well as improvements in rheological (flow) parameters are evidenced in animal and both open and placebo-controlled human studies. [5,7,15,35,41]
7. **Anti-tumor.** Systemic enzyme support may reduce the metastatic potential or tumor cells [15] and can destroy the net which connects tumor cells with each other and with the endothelium and cause a proteolysis of tumor cell membranes. [12]
8. **Antioxidant.** The antioxidant properties of the formulation may decrease the oxidative stress observed in autoimmune diseases, kidney disease and other conditions. [42-44]

Formulation Composition

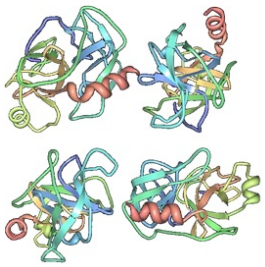
The formulation that has been shown to be clinically effective is composed of 270mg of bromelain, 300 mg of rutoside trihydrate (rutin) and 144 mg of trypsin per three pH resistant enteric coated tablets of **Wobenzym® PS** or two pH resistant enteric coated tablets of **Wobenzym® Plus**.



Bromelain
Enzyme Commission number: 3.4.22.32 [45]
Protein Data Bank Code: 1W0Q [46]
Chemical Abstracts Service number: 9001-00-7
Stem bromelain is the most abundant cysteine endopeptidase (breaks peptide bonds inside protein molecules) from the stem of the pineapple plant (*Ananas comosus*). It is distinct from the bromelain found in the pineapple fruit (EC 3.4.22.33). The geometry and the reactivity of the catalytic site are different from those of other cysteine proteinases. Broad specificity for cleavage of proteins, but strong preference for Z-Arg-Arg-|-NHMec among small molecule substrates. [45]
Bromelain is a protease that splits peptide bonds formed by the amino acids lysine, alanine, tyrosine and glycine. [47]



Rutoside Trihydrate (Rutin)
Chemical Abstracts Service number: 250249-75-3
Formula: C27H30O16·3H2O
MOL WT.: 664.59
Synonyms: Rutoside; Sophorin; Vitamin P; Quercetin-3-rutinoside; Violaquercitrin; Rutosidum;
Chemical Name: 3-[[6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl] oxy]-2- (3,4-dihydroxyphenyl)- 5,7-dihydroxy-4H-1-Benzopyran-4-one
Description: Rutin is the rutinose glycoside form of quercetin. It is a bioflavonol having aromatic trimeric heterocyclic structure. It is a naturally occurring pigment. It is a yellow to greenish crystalline powder melting at 190 C.
Rutin increases the strength of the walls of the blood capillaries and regulates their permeability so as to normalize pathologically increased vessel permeability. It is not a dietary essential but is known to have beneficial effects on capillary disorders. It also has antioxidant activity, as well as anti-inflammatory, antihistaminic and antiviral properties. [48,49]

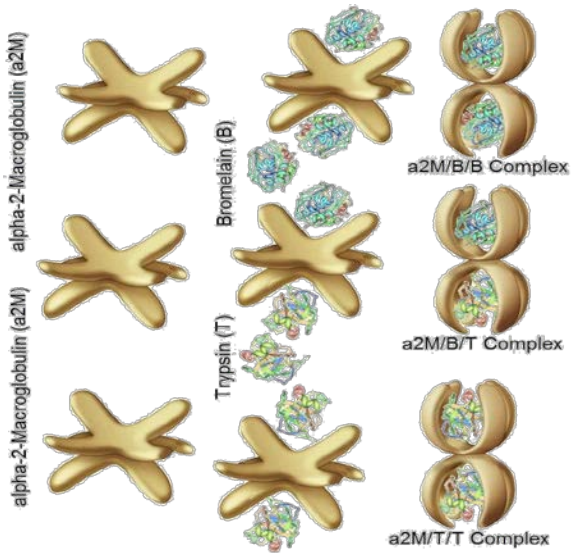


Trypsin
Enzyme Commission number: 3.4.21.4 [45]
Protein Date Bank Code: 1S81 [46]
Chemical Abstracts Service number: 9002-07-7
Description: Trypsin is an animal serine endoproteinase which breaks peptide bonds inside protein molecules. It is obtained from the pancreas of pigs by repeated refining and subsequent activation of the proenzyme trypsinogen.
Trypsin is a protease that predominantly cleaves peptide chains at the carboxyl side of the amino acids lysine or arginine, except when either is followed by proline. [47]

The high potency standardized bromelain, rutin and trypsin formulation is protected from stomach acid by a special enteric coating. This allows high levels of these activated proteolytic enzymes to be absorbed by the mucosal membrane of the intestine.

a2M Activation

alpha-2-macroglobulin (a2M)) is a high molecular weight plasma glycoprotein that comprise as much as 8-10 % of total serum protein. a2M functions as a binding, carrier, and targeting protein. It binds host or foreign peptides and particles, thereby serving as humoral defense barriers against pathogens in both the plasma and the tissue. [50]
The proteolytic enzymes tryspin and bromelain, once absorbed, will preferentially complex to the ***bait region*** of alpha-2-macroglobulin (a2M)), a high molecular weight plasma glycoprotein, to create α-2-macroglobulin-protease complexes. [51,52]
This trapping of 2 protease molecules to the a2m changes the configuration of α-2-macroglobulin so that the newly **activated α-2-macroglobulin-protease complex** now has increased binding capacity for certain cytokines [53], 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 [54] and facilitates the degradation and clearance of the amyloid beta peptide (A beta), a major component of senile plaques in Alzheimer's patients. [55-60]



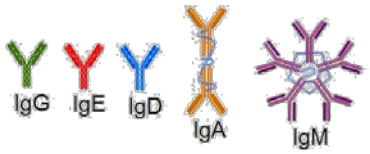
Inflammation Mediators

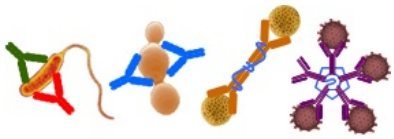
Exogenous mediators of inflammation
Substances referred to as exogenous mediators of inflammation are best described as foreign substances that initiate an inflammatory immune response typically by inducing endogenous mediators of inflammation.

Bacterial, viral, parasitic, fungal and **mycobacterial pathogens** and the **toxins** they produce can act as exogenous mediators of inflammation. These substances are antigenic and promote the generation of antibodies, which are endogenous mediators of inflammation. Other antigenic substances, such as pollen, may also initiate an inflammatory immune response and act as mediators of inflammation.

Endogenous mediators of inflammation

The endogenous mediators of inflammation are predominantly proteins and glycoproteins produced from within the immune system itself or other body systems as a response to infection or trauma.

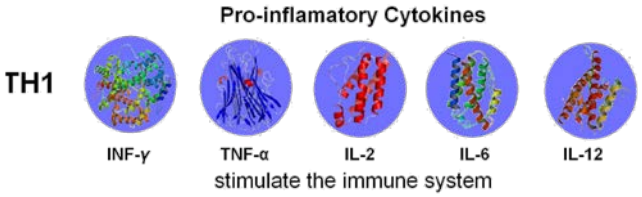




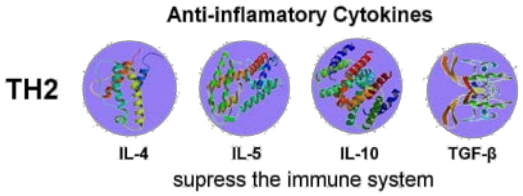
Antibodies (also known as immunoglobulins) are produced by specific white blood cells as a response to antigen exposure. Antibodies promote the activation of complement proteins (which promote pathogen death) and induce cytokine release. Antibodies are also called immunoglobulins and present in five different isotypes known as IgG, IgE, IgD, IgA & IgM. Autoantibodies are immunoglobulins which inappropriately target and damage tissues and organs of the body. Decreasing autoantibodies arrests autoimmune disease.

Circulating Immune Complexes (CICs) are formed when antibodies bind to antigens. They are elevated in a number of autoimmune conditions, infectious diseases, and cancers, as well as most immunologically mediated illnesses. They are noted in a number of conditions that adversely affect joint health, circulatory health, skin health, liver health, glucose health and heart health.

Cytokines are secreted as a response to infection or inflammation caused by the exogenous mediators of inflammation, or as a response to trauma. These cytokines are produced de novo in various cells as a direct response to stimulation of the immune system. Cytokines are signaling proteins and glycoproteins involved in cellular communication, and produced by a wide variety of cells. They are typically subdivided into two categories, Th1 & Th2. A balanced between Th1 and Th2 responses is best for optimal health.



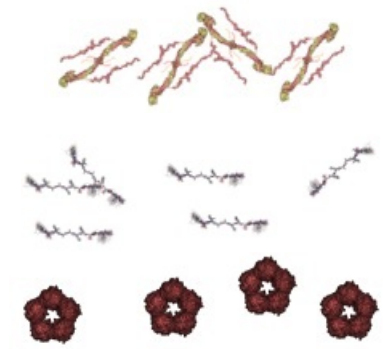
Th1 cytokines tend to produce the pro-inflammatory responses involved in antibacterial and antiviral responses. Excessive Th1 responses can lead to uncontrolled tissue damage and may perpetuate autoimmune responses. A relative excess in Th1 is observed in acute inflammation.



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 observed in chronic inflammation.

Other endogenous mediators of inflammation

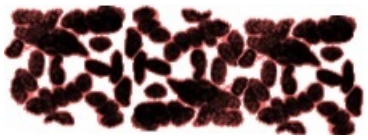
In addition to cytokines, other endogenous proteins and glycoproteins mediate inflammation and typically affect cytokine secretion.



Fibrin is a fibrous protein involved in the clotting of blood that acts as an inflammation mediator in response to injury or infection. Fibrin induces the pro-inflammatory cytokines IL-6 and TNF-α. Excessive fibrin increases risks of clots in the brain and heart. Excessive fibrin can accumulate in tissue and inhibit healing, and it can also hide cancer cells from the immune system.

Amyloid is an endogenous fibrous protein that may be induced by TNF-α. It also upregulates the pro-inflammatory cytokines TNF-α and IL-1β. It can accumulate in tissues and may play a role in a number of neurodegenerative diseases.

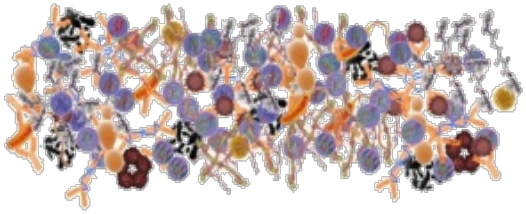
C-Reactive Protein (CRP) is a protein that becomes elevated with inflammation. It is induced by the pro-inflammatory cytokines TNF-α and IL-6. Elevated levels are associated with increased risk of diabetes and heart disease.



Damaged proteins and cellular debris including proteins destroyed by glycosylation, oxidation and cellular debris from apoptosis make up a class of proteins and glycoproteins that can contribute to inflammation by up-regulating cytokine production.

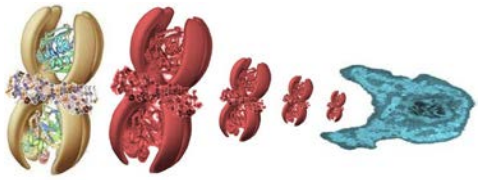
Total Burden of Inflammatory Mediators

Collectively, the various mediators of inflammation drive a number of processes, such that they can easily exceed the needs of the body to protect itself from pathogens, and contribute to the destruction of healthy tissue if their levels and actions are not modulated. Immunomodulation – the modifying, controlling and tempering of the immune system – is very dependent upon the binding to, and removal of the excessive cytokines, immunoglobulins, fibrin, amyloid and CRP and other inflammatory mediators that are created as a response to inflammation.



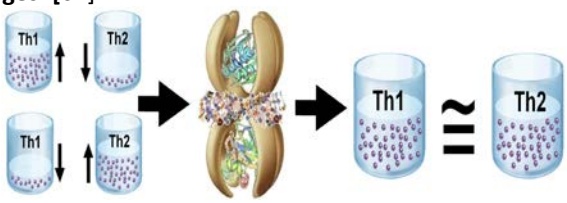
Binding & Clearance of Inflammatory Mediators

Binding of Inflammatory Mediators: Activated α-2-macroglobulin-protease complexes bind excessive interstitial and intravascular cytokines [53], immunoglobulins [62,63], fibrin [64], CRP [65], amyloid beta proteins [55-60], cell debris, and proteins damaged by oxidative stress and glycosylation. [54] These inflammatory mediators are bound near the central core of the activated α2M to regions that were not exposed in the native, non-activated form of α2M.



Clearance of Activated α2M complexes & Inflammatory Mediators: The alpha-2-macroglobulin-proteinase complexes are activated for receptor mediated endocytosis and are readily removed by hepatic α-2M-receptors (α-2M-R) [53], as well as other cells expressing α-2M-R, such as macrophages. The alpha 2-macroglobulin-proteinase complexes promote macrophage locomotion and chemotaxis [66], such that the **activated alpha 2-macroglobulin-proteinase complexes and the inflammatory mediators bound to the complex are cleared from the circulation very quickly by macrophages. [**67]

Immunomodulation: The binding removal of cytokines and other mediators of inflammation allows cytokine levels to be in their optimal physiologically balanced state. [53,68,69] This immunomodulation decreases the consequences of chronic inflammation such as degenerative conditions and proliferative disorders, which are associated with increased morbidity and mortality [53,70].



Immunomodulation prevents the destructive consequences of excessive Th1 cytokines during acute inflammation as well as the onset and progression of autoimmune diseases that typically occur with excessive Th1 cytokines. [68] Immunomodulation also decreases development and progression of allergies and atopy (asthma, eczema, allergic rhinitis & allergic conjunctivitis) that typically manifest with a chronic excess of Th2 cytokines. [70]

Clinical Applications

The formulation used in **Wobenzym® PS** and **Wobenzym® Plus** is clinically effective in a broad range of conditions due to its immunomodulatory, anti-inflammatory, anti-edema, analgesic, fibrinolytic, thrombolysis, antitumor and antioxidant properties. Dozens of randomized, blinded and placebo studies have evidenced the specific formulation can be used in various clinical specialties, including the following:

Andrology, Men's Health
At a dosage of 2 tablets t.i.d., 17 patients with bacterial prostatitis and 23 with abacterial prostatitis showed 'superiority of the enzyme preparation" over placebo in a double blind study. [71,72]

Arthritis, Rheumatology

Osteoarthritis: In a number of randomized, controlled, single-blind and double-blind studies the formulation (2 tablets t.i.d.) was considered be considered as an effective and safe alternative to nonsteroidal antiinflammatory drugs such as diclofenac in the treatment of active osteoarthritis of the knee, hips, and shoulder. [20,32,73-75,92]

Rheumatoid Diseases: In a multicentric, controlled, double-blind, randomised, clinical trial the formulation (2 tablets t.i.d.) was found to be as effective as sulfasalazine. [76] Treatment success was higher in rheumatic disease patients treated with the formulation when compared to NSAIDs with much less adverse events when compared with conventional doses of NSAID. [33] The formulation turned out to be more effective than NSAIDs in the treatment of activated, inflammatory - degenerative spinal and joint diseases, fibromyalgias and other rheumatic soft tissue diseases. [77] Animal studies also showed similar results when compared to ibuprofen. [93]

Reactive Arthritis: Reactive arthritis (adjuvant arthritis) is an autoimmune condition that develops in response to an infection in another part of the body, treated adjuvantly with the formulation showed faster relief of manifestations of joint lesion syndrome, decreased laboratory evidence of disease activity and normalization of interferon profile. In addition, the effect of antibacterial drugs was improved and chlamydia elimination was more effective. [24, 91]

Fibromylagia: Based on controlled, multicentric, retrospective analysis of therapeutical data the formulation turned out to be more effective than NSAIDs in the treatment of fibromyalgias and other rheumatic soft tissue diseases. [33,77]

Cardiology
At doses corresponding to the mean therapeutic dose for men proteolytic enzymes palliated pathological changes in the course of experimental atherosclerosis. [78] Arteriosclerosis and arterial wall remodeling were inhibited in other experimental models. [1] These findings are consistent with clinical observations that demonstrate antiatherogenic and fibrinolytic activity in humans given systemic enzymes. [69,79-81]

Dentistry
When the formulation is given before extraction, there is a shortening in the time of edema and pain in the extraction place and also the shortening of healing time. [7]

Diabetology
A clinical pilot study in patients with diabetic nephropathy demonstrated that at a dosage of 2 tablets t.i.d. the formulation reduced elevated levels of both serum and urine IL-6, a cytokine that induces over expression of TGF-b, the main trigger for the elevated protein synthesis and an inhibition of protein degradation associated with diabetic nephropathy. Animal studies also evidenced a decrease in TGF-b with decreased renal degradation. [8,16,82]

Hepatology
In an open, randomized, clinical pilot trial, hepatitis C patients treated with the formulation showed improvement in liver enzymes, and superiority to ribavirin and a-interferon. [4,83]

Immunology & Infectious Diseases
In a double-blind, randomized, controlled phase III study, children aged one month to 12 years with sepsis were treated with 1 tablet of the formulation per 10 kg of body weight as an adjuvant to antibiotic therapy. Compared to antibiotic alone, the group showed a faster reduction in fever, improvement of Glasgow coma scale and ability to resume oral feeding, with no deaths in the enzyme treated group. The study suggests that the formulation has a place as an adjuvant with antibiotics and supportive treatment for early improvement of pediatric patients with sepsis. [84]

Lymphology
The formulation normalizes lymphatic circulation in the affected area restores the transporting capacity of lymphatic system. [5,85] Even in the stage III and IV lymphedema the formulation significantly improves nutrient supply to already induced and sclerotized tissue. [5]

Nephrology

Kidney Stones: Use of the formulation (2 tablets q.id. x 4 wks) as an adjuvant in patients suffering from nephrolithiasis (kidney stones), complicated by a chronic pyelonephritis resulted in non-complicated healing of postsurgical wound, no chronic pyelonephritis deterioration, faster functional and anatomical patency of urinary tract and a marked decrease of concretion relapses in a 1-year-observation. [86] Patients treated with the formulation showed a lower incidence of kidney stone recurrence. [87]

Chronic Kidney Disease: In a double-blind placebo controlled pilot study patients on the formulation had showed a decline in albuminuria and serum creatinine. [82] The formualtion also decreases the auumulation of advanced glycation end (AGE) products. [82,90] In animal studies, the formulation ameliorated development of tubulointerstitial fibrosis and the progression of chronic renal failure [88] and decreased clinical signs and morphologic lesions of immune complex glomerulonephritis, reduces the immune deposits, and prevents or retards the progression to end stage renal disease. [89]

Neurology
Use of the formulation for 1 to 3 years decreased the incidence and degree of MS complications, increased the duration of remissions, and slowed the progression of the illness in 74 patients with remitting, remitting-progressive, and secondary progressive course of multiple sclerosis. [6] There is a stabilization of neurological impairment and improved activities of daily living. The findings are causatively linked to a decrease in inflammatory activity. [11]

Oncology
The formulation triggered the formation of intermediate forms of a2-macroglobulin displaying high affinity to TGF-b in volunteers. [94] High concentrations of TGF-b are reduced due to enhanced clearance of a2-macroglobulin-TGF-b complexes, which cab benefit certain cancers accompanied by excessively high TGF-b concentrations. [70]
As an adjuvant, 2 tablets, t.i.d. alleviated the consequences of radiation-induced epitheliitis in patients with laryngeal cancer. [36] It also decreases post-irradiation reactions in breast cancer patients. [12]

Otolaryngology
The formulation showed the best result in treating both anterior acute uveitis and chronic anterior uveitis mostly associated with juvenile chronic arthritis. [95] The formulation as an adjuvant significantly clinical outcomes in children suffering from chronic secretory otitis and decreased the negative influence on a speech development. [13]

Pulmonology & Respiratory Diseases
In children (3-15 y/o) showing a high sickness rate and abnormal immunoglobulin levels, adjuvant use of the formulation (1 tablet per 10 kg of body weight) resulted in reduction of both frequency and severity of diseases. [63]

Traumatology, Surgery
In experimentally induced hematomas, 6 tablets/day of the formulation is as effective as the dose of 12 tablets/day, and significantly better than 2 tablets/day or placebo. [96,97,21] Researchers concluded that the investigated preparation is an effective therapeutic agent for injuries resulting in pain and hematoma. [21] A very marked anti-oedematous effect of the formulation (3 tablets, t.i.d.) was noted in postoperative period after surgical repair of fractured long bones with metal plates, pins, rods, wires or screws. [37] The formulation significantly improves the outcomes of traumatological surgery, by reducing post-traumatic and postoperative swelling. [34,98] The formulation is an effective and safer alternative to NSAIDs in the post-operative rehabilitation phase after artificial knee implantation. [27] Pre-surgical dosing for 3 to 6 days with 5 tablets t.i.d., and postsurgical dosing at 2 tablets t.i.d. was able to quickly restore the impaired function of affected upper and lower extremities. [22] Postoperative edema was significantly decreased in patients undergoing septoplasty. [99] The formulation may decrease the loss of bone mineral density. [100]

Urology
In patients with relapsing urinary tract infections responding poorly to antibiotic therapy, the formulation significantly decreased healing time compared to a placebo and showed a reduction of ESR and leukocytes that correlated with the decrease of inflammation. [101]
In a randomized, placebo controlled, clinical, double-blind, multicenter phase III study, the formulation plus antibiotics had outcomes that were superior than antibiotics plus placebo in patients with acute hemorrhagic cystitis. [102]

Vascular Medicine
In patients presenting with acute thrombophlebitis and postthrombophlebitic syndrome, the formulation demonstrated a decrease of pain, reduction of edema and throphic ulcers, and improvement of microcirculation. [35]
At a dosage of 2 tablets, t.i.d. clinical effect was pronounced with regression of chronic venous insufficiency in postphlebitic syndrome. [39] The formulation significantly reduces plasma viscosity and erythrocyte aggregation and increases blood fibrinolytic activity. [40,5]

Therapeutic Dosing

Optimal Dosage: The preponderance of clinical studies have shown the formulation to be effective at a dosage of six **Wobenzym® PS** tablets per day, taken as either three tablets twice a day, or two tablets three times a day. The dosage for **Wobenzym® Plus** would be four tablets per day, taken as two tablets twice a day. This dosage has been used to treat osteoarthritis [28,30,74,75], rheumatoid arthritis [23,33,76], tendonitis [29], chronic prostatitis [71,72], relapsing urinary tract infections [101], recurrent respiratory tract infection [63], sepsis [84], diabetic nephropathy [82], multiple sclerosis [6], trauma [22,25,26,96], postphlebitic syndrome [39], as well as pre & post surgically [34].
Surgical Dosage: One group dosed 3 tablets of **Wobenzym® PS**, five times daily for 2 to 6 days before surgery, followed by 3 tablets twice a day after surgery. [22] Another group dosed, 3 tablets three times day for the first 3 days after surgery. Followed by 2 tablets 3 times/day. [34] Two tablets of **Wobenzym® Plus** can be used in place of three tabltes of **Wobenzym® PS**.
Pediatric Dosage: In two separate conditions, children aged 1 month to 15 years were given 1 tablet per 10 kg/body up to a maximum of six tablets for a duration of days to six months. [84,63] The **Wobenzym® PS** equivalent would be 1 tablet per 15 kg/body weight up to four tablets.

References

References for the reference numbers in this specific section are listed in the end of the book under “PROFESSIONAL SYSTEMIC ENZYME SUPPORT: Advanced Immunomodulation with Professional Strength Systemic Enzyme Support Poster”.

AN EXHAUSTIVE REVIEW OF INTERNATIONAL LITERATURE.

During my studies into Wobenzym® formulations, I soon came to realize that these formulations are the most researched "supplements" in the world. I say "supplements" because here in America, they are recognized as a natural supplement. However, as I studied the international literature, I found that the Wobenzym® formulations were used in hospitals, and clinics throughout the world. In many cases the Wobenzym® formulations were used alone. However, in a number of cases the formulations were used right along with prescription medications such as antibiotics and heart medications to make those medications more effective.

Using Wobenzym® formulations with medications is called "adjuvant" therapy, which means the Wobenzym® formulations were used as an adjunct with the prescription medication. Sometimes the use of a Wobenzym® formulations with prescription medicine is called "complex therapy". When used in this fashion, the phrase "complex therapy" means a therapy made up of interrelated parts.

The exhaustive review of international literature resulted in a compilation of over 160 studies on Wobenzym® formulations. Those studies have primarily been categorized in this book based on the specific conditions they treat. Some of the studies are mentioned later in this book, in the section about How Systemic Therapy Works.

There will be more information later in this book on the science of how Wobenzym® formulations work through their interactions with the immune system. However, at that time, we will now turn our attention to the research on specific conditions.

If you do not see specific information about the condition you are concerned about, you will learn in this book how Wobenzym® formulations work, and how they can be used for any condition that involved immune dysfunction. The section on How Systemic Therapy Works, which is presented later in the book, will give you insights and guidelines into using the Wobenzym® formulations either alone, or in the complex treatment (adjuvant) of any condition.

Understanding the Literature & Names of Wobenzym® Formulations

As you read through the various studies, you will notice different names are used to describe the various Wobenzym® formulations. When the word Wobenzym® is used, it is referring to the product we know as Wobenzym® N.

In foreign countries the different formulation is called "Phlogenzym". That formulation is now called Wobenzym® PS or Wobenzym® Plus, depending on the size of the tablet. Three tablets of Wobenzym® PS are equal to two tablets of Wobenzym® Plus.

While the name Wobenzym® or Phlogenzym oftern occur is the title or the abstract of the study, there are some cases in which the product name only occurs in the MeSH Terms (Medical Subject Headings).

The words Wobenzym® or Phlogenzym occur almost 100 times in www.PubMed.gov searches. Other resources for research compilation include foreign databases.

RESEARCH ON SPECIFIC CONDITIONS

This section will present the research on the use of Wobenzym® formulations for a number of conditions. In each section I try to share some of my personal experiences of using Wobenzym® formulations in the treatment of these conditions.

Understanding the research:

Keep in mind that much of this research is from international studies. So, it is research done outside of the United States of America. This research may have been as close a Canada, or as far away as Russia. Much of the research has been translated from its original language. Therefore, the grammar and sentence structure may be a little different from research that originates in America. I encourage you the reader to look past the grammar and sentence structure, and focus on the facts that are presented on the use of Wobenzym® formulations for a wide range of conditions.

Also, in other parts of the world Wobenzym® formulations have different names. The best example is that Wobenzym® PS is called Phlogenzym® in some other countries. For each conditions I will show how the research can be translated into using specific Wobenzym® formulations commonly available in America, and throughout the world today. Later in the book, I will share a summary of research on the specific Dosage Guidelines for the various Wobenzym® formulations, which will include details on how to switch from one Wobenzym® formulation to another Wobenzym® formulation.

ALZHEIMER'S DISEASE

The nervous system is just as sensitive to the assaults of systemic inflammation as other body systems. Inflammation plays a critical role in the development of debilitating neurological conditions such as Alzheimer's disease, which some doctors describe as "the brain on fire". In fact, it is now more appropriate to call Alzheimer's and inflammatory disease. The phrase "degenerative brain disease" does not appropriate describe the fact a root cause is the active inflammation taking place in the brain.

We now know that systemic inflammation increases production of the pro-inflammatory cytokine TNF-alpha (tumor necrosis factor alpha).

A recent study of three hundred patients noted that increased serum levels of TNF-alpha due to systemic inflammation are associated with increased rate of cognitive decline.

Research has shown, without a doubt, that Wobenzym® decreases serum levels of TNF-alpha. As we saw in the rheumatoid arthritis studies, patients treated with Wobenzym® have TNF-alpha levels less than half the levels seen in untreated patients. This decrease is the pro-inflammatory cytokine TNF-alpha is one of the mechanisms by which Wobenzym® can decrease the progression of Alzheimer's disease.

I cannot overemphasize how important it is to have TNF-alpha levels lowered. If the levels of that pro-inflammatory cytokine are not kept in check, we see increased production of amyloid beta peptides, the main component of the plaques that appear in the brains of Alzheimer's patients. By decreasing TNF-alpha, Wobenzym® can decrease the formation of those dangerous amyloid beta peptides.

Another important finding is that Wobenzym® can promote the breakdown and clearance of these amyloid beta peptides. A number of studies show that when alpha-2-macroglobulin is activated – which we discussed earlier as a primary action of Wobenzym®, the amyloid beta peptides are broken down, and removed from tissues at an accelerated rate.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Using Wobenzym® for Treating Diseases of Brain & Nervous System

What the literature says about Wobenzym® and ALZHEIMER'S DISEASE

Alpha 2-macroglobulin-mediated degradation of amyloid beta 1--42: a mechanism to enhance amyloid beta catabolism.

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.

Peptides derived from proteolytic degradation of the amyloid precursor protein, e.g., amyloid beta (A beta), are considered to be central to the pathology of Alzheimer's disease (AD). Soluble amyloid beta is present in measurable concentrations in cerebrospinal fluid and blood. There are indications that soluble amyloid beta present in circulation can cross the blood-brain barrier via transcytosis mediated by brain capillary endothelial cells. It implies that amyloid beta originating from circulation may contribute to vascular and parenchymal amyloid beta deposition in AD. Enhancing of A beta catabolism mediated by proteolytic degradation or receptor-mediated endocytosis could be a key mechanism to maintain low concentrations of soluble amyloid beta. To launch A beta clearance, we have exploited the amyloid beta-degrading activity of diverse alpha 2-macroglobulin (alpha 2-M)-proteinase complexes. Complexes with trypsin, alpha-chymotrypsin, and bromelain strongly degrade (125) insoluble amyloid beta 1--42 whereas complexes with endogenous proteinases, e.g., plasmin and prostate-specific antigen, were not effective. A beta degradation by the complexes was not inhibited by alpha 1-antichymotrypsin and soybean trypsin inhibitor which normally would inactivate the free serine proteinases. A prerequisite for A beta degradation is its binding to specific binding sites in alpha 2-M that may direct A beta to the active site of the caged proteinase. Ex vivo, enhanced degradation of (125) insoluble amyloid beta 1--42 in blood could be achieved upon oral administration of high doses of proteinases to volunteers. These results suggest that up-regulation of A beta catabolism could probably reduce the risk of developing AD by preventing A beta accumulation in brain and vasculature.

External Link: PMID: 11161627

Degradation of amyloid beta-protein by a serine protease-alpha2-macroglobulin complex.

Qiu WQ, Borth W, Ye Z, Haass C, Teplow DB, Selkoe DJ. Degradation of amyloid beta-protein by a serine protease-alpha2-macroglobulin complex. 1: J Biol Chem. 1996 Apr 5;271(14):8443-51. Department of Neurology, Harvard Medical School, Boston, Massachusetts 02115, USA.

Progressive cerebral deposition of the amyloid beta-peptide (Abeta) is an early and constant feature of Alzheimer's disease. Abeta is derived by proteolysis from the beta-amyloid precursor protein. beta-Amyloid precursor protein processing and the generation of Abeta have been extensively characterized, but little is known about the mechanisms of degradation of this potentially neurotoxic peptide.

We identified and purified a proteolytic activity in culture medium that can degrade secreted Abeta but not larger proteins in the medium. Detection of the activity in conditioned medium required the presence of fetal bovine serum and the passage of the cells with a pancreatic trypsin preparation. Its inhibitor profile showed that the activity was a serine protease other than trypsin or chymotrypsin. The protease occurs as a stable approximately 700-kDa complex with the inhibitor, alpha2-macroglobulin (alpha2M), that retains activity against small substrates such as Abeta.

Its NH2-terminal sequence suggests that the protease is previously unidentified. Our results indicate that the Abeta-degrading protease we have detected is a non-trypsin component of a pancreatic trypsin preparation or else derives from a zymogen in serum that is activated by a protease in the latter preparation. Because Abeta-bearing plaques in Alzheimer's disease brain contain both alpha2M and receptors of alpha2M-protease complexes, the same or a similar alpha2M-protease complex could arise in vivo and play a role in Abeta clearance.

External Link: PMID: 8626544

alpha2-Macroglobulin as a beta-amyloid peptide-binding plasma protein.

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. Division of CNS Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, U.S.A.

The beta-amyloid peptide (A beta) is a normal proteolytic processing product of the amyloid precursor protein, which is constitutively expressed by many, if not most, cells. For reasons that are still unclear, A beta is deposited in an aggregated fibrillar form in both diffuse and senile plaques in the brains of patients with Alzheimer's disease (AD). The factor(s) responsible for the clearance of soluble A beta from biological fluids or tissues are poorly understood. We now report that human alpha2-macroglobulin (alpha2M), a major circulating endoproteinase inhibitor, which has recently been shown to be present in senile plaques in AD, binds 125I-A beta (1-42) with high affinity (apparent dissociation constant of 3.8 x 10(-10) M). Approximately 1 mol of A beta is bound per mole of alpha2M. Both native and methylamine-activated alpha2M bind 125I-A beta (1-42). The binding of 125I-A beta (1-42) to alpha2M is enhanced by micromolar concentrations of Zn2+ (but not Ca2+) and is inhibited by noniodinated A beta (1-42) and A beta (1-40) but not by the reverse peptide A beta (40-1) or the cytokines interleukin 1beta or interleukin 2. alpha1-Antichymotrypsin, another plaque-associated protein, inhibits both the binding of 125I-A beta (1-42) to alpha2M as well as the degradation of 125I-A beta (1-42) by proteinase-activated alpha2M. Moreover, the binding of 125I-A beta (1-42) to alpha2M protects the peptide from proteolysis by exogenous trypsin. These data suggest that alpha2M may function as a carrier protein for A beta and could serve to either facilitate or impede clearance of A beta from tissues such as the brain.

External Link: PMID: 9202323

Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation.

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. 1: Proc Natl Acad Sci U S A. 1998 Mar 17;95(6):3275-80. Biotechnology Group and the Central Nervous System Disease Group, Hoechst Marion. Roussel, Inc., P.O. Box 6800, Bridgewater, NJ 08876-0800, USA.

We have used the yeast two-hybrid system to isolate cDNAs encoding proteins that specifically interact with the 42-aa beta-amyloid peptide (Abeta), a major constituent of senile plaques in Alzheimer's disease. The carboxy terminus of alpha2-macroglobulin (alpha2M), a proteinase inhibitor released in response to inflammatory stimuli, was identified as a strong and specific interactor of Abeta, utilizing this system. Direct evidence for this interaction was obtained by co-immunoprecipitation of alpha2M with Abeta from the yeast cell, and by formation of SDS-resistant Abeta complexes in polyacrylamide gels by using synthetic Abeta and purified alpha2M. The association of Abeta with alpha2M and various purified amyloid binding proteins was assessed by employing a method measuring protein-protein interactions in liquid phase. The dissociation constant by this technique for the alpha2M-Abeta association using labeled purified proteins was measured (Kd = 350 nM). Electron microscopy showed that a 1:8 ratio of alpha2M to Abeta prevented fibril formation in

solution; the same ratio to Abeta of another acute phase protein, alpha1-antichymotrypsin, was not active in preventing fibril formation in vitro.
These results were corroborated by data obtained from an in vitro aggregation assay employing Thioflavine T. The interaction of alpha2M with Abeta suggests new pathway(s) for the clearance of the soluble amyloid peptide.
External Link: PMID: 9501253

Beta-amyloid peptide binds equivalently to binary and ternary alpha2-macroglobulin-protease complexes.

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. Department of Biochemistry and Molecular Genetics University of Virginia School of Medicine, Charlottesville, Virginia, 22908, USA.

alpha2-Macroglobulin (alpha2M) is a protease inhibitor that has separate binding sites for transforming growth factor-beta (TGF-beta) and beta-amyloid peptide (Abeta), both of which have been identified in the beta2M sequence. In the 3D-structure of alpha2M, TGF-beta occupies the alpha2M central cavity, overlapping with the space that can accommodate up to two molecules of protease. As a result, ternary alpha2M-protease complexes (2 mol protease/mol alpha2M) have been reported to not bind TGF-beta. The goal of the present study was to test whether binding of Abeta to alpha2M is controlled by steric constraints imposed by associated proteases, similarly to TGF-beta. We confirmed that binary alpha2M-trypsin complex (1 mol trypsin/mol alpha2M) binds increased amounts of TGF-beta1, compared with native alpha2M, while ternary alpha2M-trypsin complex binds substantially decreased amounts of TGF-beta1. By contrast, Abeta-binding to binary and ternary alpha2M trypsin complex was equivalent. In both cases, binding was substantially increased compared with the negligible level observed with native alpha2M. Plasmin is a large protease (Mr approximately 82,000) that substantially occupies the alpha2M central cavity; however, alpha2M-plasmin complex also bound increased amounts of Abeta, compared with native alpha2M. We conclude that Abeta accesses its binding site, in alpha2M, from outside the alpha2M central cavity. The TGF-beta- and Abeta-binding sites are spatially separated not only in the primary sequence of alpha2M, but also in the 3D-structure.
External Link: PMID: 16003950

Alpha2-macroglobulin enhances the clearance of endogenous soluble beta-amyloid peptide via low-density lipoprotein receptor-related protein in cortical neurons.

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. 1: J Neurochem. 1999 Oct;73(4):1393-8. Alzheimer Research Unit, Massachusetts General Hospital and Harvard Medical School, Boston 02129, USA.

Apolipoprotein E and alpha2-macroglobulin (alpha2M) are genetic risk factors for late-onset Alzheimer's disease, and both bind a cell surface receptor, the low-density lipoprotein receptor-related protein (LRP). To investigate the role of LRP on preventing the accumulation of beta-amyloid peptide (A beta), we examined the effects of alpha2M on the clearance of endogenous A beta. Studies were performed in primary Tg2576 transgenic mouse cortical neuronal cultures expressing human mutant amyloid precursor protein (APP) 695. This system allowed us to follow endogenous A beta using immunoblots to detect monomeric forms of the peptide. A beta and APP levels were measured in conditioned media. We found that activated alpha2M (alpha2M*) substantially decreased soluble A beta levels and had no effect on secreted or full-length APP levels. Native alpha2M, which is not a ligand for LRP, did not affect A beta levels. The receptor-associated protein, which inhibits interaction of all ligands with LRP in vitro, prevented alpha2M*-induced decreases of soluble A beta levels. These data suggest that alpha2M* affects soluble A beta clearance rather than A beta production. Further studies showed that similar A beta clearance via an LRP-mediated pathway was observed after treatment with another LRP ligand, lactoferrin. Taken together, these data demonstrate that alpha2M* enhances the clearance of soluble A beta via LRP in cortical neurons.
External Link: PMID: 10501182

ANGINA

When Wobenzym® was added to the treatment of **angina pectoris** (chest pain due to heart problems), the frequency and intensity of angina attacks were reduced and tolerance to physical load was increased. A drop in pro-inflammatory cytokine levels was also noted.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Carviovascular and Lymphatic Systems & Wobenzym®

What the literature says about Wobenzym® and ANGINA PECTORIS

Systemic enzyme therapy in the complex treatment of angina pectoris.

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 - ISSN 0255-9625 218 K/375 (19-05-3) Postgraduate Medical Academy, St. Petersburg, Russia.

Summary: Complex treatment of stable angina pectoris (b-adrenoblockers, calcium antagonists, aspirin, and nitrates) with systemic enzyme therapy positively affected the clinical course of the disease. The frequency and intensity of angina pectoris attacks were reduced and tolerance to physical load was increased. Dynamic echocardiography revealed improved diastolic heart function.

Echodensitometric study of the myocardium in diastole showed disappearance of earlier diagnosed areas of increased ultrasonic density. The antiinflammatory, fibrinolytic and immunoregulatory effects of systemic enzyme therapy are the main mechanisms responsible for its beneficial effects.

Wobenzym® administration led to the reduction of interleukin (IL)-1b and IL-8 cytokine levels.

Tumor necrosis factor-alpha levels tended to decrease. The phagocyte concentration in monocytes and neutrophils and the nitroblue tetrazolium (NBT)-test parameters substantially increased. The effect of systemic enzyme therapy on coagulation, fibrinolysis and the rheological properties of blood was evaluated, revealing an increase in activated partial thromboplastin time index from 0.85 ± 0.04 to 0.97 ± 0.02 ($p<0.05$), plasma fibrinolytic activity and a decrease in active platelets. In conclusion, administration of systemic enzyme therapy in patients with angina pectoris is pathogenetically justified and should be used in the complex treatment of coronary heart disease.

ATHEROSCLEROSIS

Wobenzym® also **decreased cholesterol** an average of 24% after one month of therapy. It also lowered the levels of atherogenic lipoproteins as well as inflammatory markers associated with **atherosclerosis**.

It is important to note that in addition to lowering excessive lipids, controlling inflammation in cardiovascular disease is also recognized as an important benefit of systemic enzyme support.

One study showed that in patients who had suffered a myocardial infarction, **cholesterol dropped** 12% and lipoproteins drops 16% **after taking 9 Wobenzym® tablets a day for 10 days**. A second group in the same study had a 24% drop of cholesterol and 31% drop of lipoproteins within one month at the same dosage. The researched also noted that the immune status of myocardial infarction (MI) patients is significantly impaired and that Wobenzym® had an immunonormalizing affect.

A parallel study of myocardial infarction patients and two groups of rabbits reported a “significant decrease of cholesterol level” in both the clinical and the experimental studies. They concluded that “it can be recommended to use Wobenzym® in complex treatment of myocardial infarction patients to reduce risk factors of reinfarction.”

A 2001 study tracked 52 patients taking Wobenzym® for 6 months. They also noted an improvement lipid levels. They also noted an improvement in cytokine levels, and concluded in postmyocardial infarction patients Wobenzym® helped improve the biochemical and immune abnormalities.

It is also notable that patients with autoimmune thyroid disease experienced lower cholesterol and triglyceride levels after being treated with Wobenzym®. Now this may be because their anti-thyroid antibody levels had dropped with Wobenzym® therapy, but it is still notable that cholesterol levels are improved in these patients.

I should also point out that improved cholesterol levels are also observed in chronic levier disease patients after they were treated with Wobenzym®.

Please see the **FREQUENTLY ASKED QUESTIONS** section on: Carviovascular and Lymphatic Systems & Wobenzym®

What the literature says about Wobenzym® and ATHEROSCLEROSIS

The effect of Wobenzym® on the atherogenic potential and inflammatory factors in postmyocardial infarction patients.

Ryabokon E., Gavrilenko T., Kovalenko V. and Kornilina E. The effect of Wobenzym® on the atherogenic potential and inflammatory factors in postmyocardial infarction patients. 3rd International Congress on Coronary Artery Disease, Lyon (France), October 2 – 5, 2000. Institute of Cardiology, Kiev, Ukraine. [Czech abstract]

Summary: The effect of systemic enzyme therapy preparation Wobenzym® on the serum atherogenicity and immunoinflammatory reactions was studied over the period of 6 months in the postmyocardial infarction patients at the rehabilitation stage. *Inclusion of Wobenzym® into the conventional treatment led to the normalization of an atherogenic potential and showed a positive effect on inflammatory process mediators.*

The systemic enzyme therapy in experimental atherosclerosis

Dosenko V.E., Zakharova V.P., Byc Y.V. The systemic enzyme therapy in experimental atherosclerosis. Experimental cardiology 2000, No. 5-6, pp. 87-94. [Russian abstract, Czech abstract]

The etiology and pathogenesis of atherosclerosis (AS), which is undoubtedly influenced by modified lipoproteins and damaged arterial wall with altered properties of blood vessel connective tissue is discussed. The goal of this study was to estimate the effect of proteolytic enzymes in the treatment and prophylaxis of AS. The elastolytic system of serum and tissues was studied.22 adult chinchila rabbits were included into the study. AS was simulated by means of feeding 0.75% cholesterol diet for 30 days. The animals were divided into three groups: I – controls fed by a standard diet, II – received only cholesterol diet, III – received cholesterol diet and Phlogenzym at doses corresponding to the mean therapeutic dose for men. After 30 days, the animals were sacrificed. Aortas were homogenized and exploited for biochemical analysis. Blood was sampled and serum was prepared. The activity of elastase was determined using a specific chromogenic substrate. The amount of total cholesterol was assayed. The stripes of aortas were fixed in HCHO and prepared for histological examination. All data were statistically evaluated by Student`s t-test.

In the course of AS modeling, a fundamental impairment of the system elastase-inhibitors was discovered. The activity of elastase (mM/g of protein or per 1 l of serum resp.), the content of a2 macroglobulin (a2 M) (mg/g of protein or g/l of serum resp.), and a1 proteinase inhibitor (mg / g of protein or g/l of serum resp.) were measured.

Changes of the coefficient inhibitors/elastase, which is a real indicator of elastolytic system, were studied.

There was no difference in the serum elastase activity between groups I and II (15.65 ± 0.64 vs. 15.67 ± 3.67), while there was a statistically significant decrease (7.64 ± 1.08) in the group III (Phlogenzym).

The level of a2 M was statistically significantly lowered in groups II and III (1.75 ± 0.16; 1.21 ± 0.23) in comparison to the control group (2.61 ± 0.16). The resulting coefficient of inhibitors/elastase was thus increased in the Phlogenzym group III (414.9) as compared to the groups I and II (232.6; 195.9). In other words, a decrease of elastolytic activity was found in serum of Phlogenzym-treated animals.

The comparison of elastase activity in aorta homogenates revealed, however, an opposite trend: there was no difference in elastase activity between groups I and II (2.52 ± 0.19 vs. 1.86 ± 0.44), while there was a statistically significant increase (5.44 ± 1.15) in the group III (Phlogenzym). The level of a2 M was statistically significantly lower in the groups II and III (5.07 ± 1.89; 5.74 ± 1.62) in comparison to the control group (9.72 ± 0.74). The coefficient of inhibitors/elastase was thus lowered in the Phlogenzym group III (1.14) as compared to the groups I and II (4.20; 3.30). In other words, again, an increase of elastolytic activity was found in the aorta tissue of Phlogenzym-treated animals.

Histopathological examination revealed morfological changes of fibrous structures of aorta, lysis of segments and loosened fibers of elastic membranes in the group II (cholesterol fed animals). Degeneration of collagen fibers was also observed. The administration of Phlogenzym had a significant effect on the elastolytic system of rabbits. The findings in animals treated by Phlogenzym were less pronounced, collagen and elastic fibers maintained its structure. The addition of proteolytic enzyme mixture palliated pathological changes in the course of experimental atherosclerosis. Elastase is generally considered to cause a degradation of intercellular proteins only. However, it may have a protective and prophylactic effect against development of AS.

Elastase operates against decrease of acetylcholin-induced relaxation and noradrenalin-induced constriction and it has the ability to lower total cholesterol. Purified pancreatic elastase (Elaszym) is authorized in Japan and it is used for prophylaxis and treatment of AS. It contributes to the decrease of arterial pressure and inhibits aging of arterial blood vessel tissues. The authors suppose that the strong effect of elastase against AS is not specific, and the same effect can be achieved by other proteolytic enzymes administered orally because they activate the same cell receptors.

Treating AS by a combination polyenzyme preparation is more advantageous than just elastase monotherapy.

AUTOIMMUNE THYROID DISEASE

Wobenzym® significantly improves autoimmune hypothyroidism (**Hashimoto's**), the most common cause of hypothyroidism. Autoimmune hypothyroidism is a condition that until now has been somewhat difficult to successfully treat due to the chronic inflammation taking place in that condition. Even after the patient's hormone levels have been brought back to normal with prescription thyroid replacement, we still see many clinical signs of hypothyroidism.
Autoimmune hypothyroidism (**Hashimoto's**) – the most common cause of hypothyroidism - is a condition that can be somewhat difficult to successfully treat due to the chronic inflammation taking place in that condition. Even after the patient's hormone levels have been brought back to normal with prescription thyroid replacement, we still see many clinical signs of hypothyroidism.
For instance, even after thyroid replacement therapy (TRT), patients can still have elevated cholesterol and triglycerides. However, when TRT patients that still had elevated cholesterol and triglycerides were given 5 Wobenzym® tablets, 3 times a day their cholesterol and triglycerides decreased. The patients that were only given thyroid replacement still had elevated cholesterol and triglycerides
We also noted that taking **Wobenzym® resulted in a reduction of autoimmune antibodies that attack the thyroid** – the anti-TG and anti-TPO antibodies. With the reduced antibodies, the thyroid is no longer under attack from the immune system, and is able to resume making thyroid hormones that way that it should.
Patients on Wobenzym® also showed a reduction of TSH levels – which is due to increased function of thyroid hormones. As a result, **patients that received Wobenzym® as part of their therapy were able to lower their dosage of thyroid medication after 3 months, or completely discontinue the thyroid medication in some cases.**
Based on what we now know, I would say that this is possible because of the beneficial effect that Wobenzym® has on the hypothalamic-pituitary-thyroid axis, its effect on the thyroid tissue itself, and its effect on the immune system - the elimination of autoimmune destruction of the thyroid.
The pro-inflammatory cytokines that we see in both autoimmune disease and in systemic inflammation have a very detrimental effect on thyroid function on so many levels. If we keep in mind that the first word in the phrase "autoimmune thyroid disease" is "autoimmune" we will have a better understanding of why **the immunomodulation properties of Wobenzym® are so effective in treating autoimmune hypothyroidism**.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Hormones & Wobenzym®

What the literature says about Wobenzym® and AUTOIMMUNE THYROID DISEASE

Wobenzym® in the complex treatment of autoimmune thyroiditis.

Kvantchakhadze R.G. Wobenzym® in the complex treatment of autoimmune thyroiditis. International Journal on Immunorehabilitation, 2002, Vol. 4, No. 1, pp. 114. [Czech abstract, Russian abstract] Research and Therapeutic Center of Rheumatology, Tbilisi, Gruzia. VIII. International Congress on Immunorehabilitation, Allergy, Immunology, and Global Net, April 21-24, 2002, Cannes, France

40 patients suffering from autoimmune thyroiditis were observed for 6 months. Patients were divided into two groups. 20 patients in the group I were treated depending on thyroid condition (euthyreosis, hypothyreosis) with L-tyroxin (25 – 100 mg daily) in combination with Wobenzym® (5 coated tablets three times a day). Patients in the group II were treated with L-tyroxin only at the above dosage.
Both groups were comparable with regard to age, sex, and clinical-laboratory parameters. All usual parameters were examined before treatment, after 1 and 3 months, and at the end of treatment. Improvement of thyroid parameters at ultrasound examination (reduction of size, improved tissue structure) and aspiration biopsy parameters (reduced number of lymphoid and plasmocytoma cells in cytologic punctuate) as well as significant decrease of blood thyreotropin level and titers of antibodies against thyreoglobulin and microsomal fraction accompanied by the improvement of subjective parameters were found in the group I after 3 months of treatment, whereas in the group II after 6 months of treatment.
In both groups of patients suffering from hypothyreosis, an impaired lipid metabolism was found.
Treatment of patients in the group I resulted in a decrease of cholesterol and triglyceride levels, whereas in patients in the group II there were no significant changes found during the treatment.
In patients in the group I dosage of L-tyroxin could be lowered after 3 months of treatment, in some cases it could even be discontinued. Under continuous Wobenzym® treatment improved clinical-laboratory parameters were maintained.
Thus, Wobenzym® was shown to be therapeutically effective in a complex therapy of autoimmune thyroiditis

BEHÇETS

Behçet's (beh-CHETS) disease, also called Behcet's syndrome, is a rare disorder that causes chronic inflammation in blood vessels throughout your body. The signs and symptoms of Behcet's disease — which may include mouth sores, skin rashes and lesions, uveitis, and genital sores — vary from person to person and may come and go on their own. Treatment aims to reduce the signs and symptoms of Behcet's disease and to prevent serious complications, such as blindness.
Patients that did not have adequate therapeutic results from conventional therapy were started on Wobenzym® therapy, which resulted in positive results in 90% of treated patients.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Eyes, Ears, Nose & Throat Conditions & Wobenzym

What the literature says about Wobenzym® and BEHÇETS

The results of long-term use of Wobenzym® in complex management of Behçet's disease.

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. Center of Rheumatology, Tbilisi, Georgia [Czech abstract]

Twenty patients (13 males and 7 females) with the confirmed diagnosis of Behcet's disease were followed-up. Average age of the patients was 41.27±2.96. The diagnosis was verified following the international criteria which were worked out by the International Study Group for Behcet's Disease (1990). As a rule, each patient had recurrent aphthous stomatitis and 2 or 3 of the following four criteria: recurrent ulcers of genital organs, eye and skin lesions, positive "pathergy" test.

The patients were administered Prednisolone at a dose of 10-15 mg/day, Azathioprine (100 mg/day), non-steroid antiinammation medicines, antiaggregating drugs etc. However, because of the absence of the expressed therapeutic effect after 1-1.5 months of the treatment Wobenzym® (Mucos Pharma, Germany) in the dose of 7 tablets three times a day was added to the scheme. Favourable dynamics of clinical manifestations, inflammatory and immune activities were observed 0.5-1 month after introduction of Wobenzym®. Significant decrease in the level of circulating immune complexes and cryoglobulins is noteworthy. Positive results (90.0%) combined with the absence of side effects and possibility to decrease the Prednisolone doses are significant success in the management of this severe disease.

DIABETES

We know that Wobenzym® can increase levels of C-peptide in autoimmune mediated diabetes, such as type 1 diabetes. In addition to showing much insulin the pancreas can still make, C-peptide decreases the progression so the common complications of diabetes, including the **diabetic nephropathy**.
We also note that systemic enzymes can decrease the formation of “advanced glycation end products” (AGEs), which are associated with diabetic nephropathy and other complications of diabetes.
In addition, abnormal cytokines levels are normalized, including transforming growth factor beta-1 (TGF-b1), and interleukin 6.
What we have come to realize, is that the complications of diabetes are strongly mediated by the immune system. We see that controlling blood sugar with insulin is not enough to prevent complications such as **diabetic nephropathy**. The abnormal cytokine levels that occur with diabetes can safely and effectively be normalized with Wobenzym®.

Please see the *Diabetic Kidney Disease Question* in the **FREQUENTLY ASKED QUESTIONS** section on:
Kidney and Bladder Conditions & Wobenzym®

What the literature says about Wobenzym® and DIABETES MELLITUS

Regular intake of Wobenzym® may prevent late complications in diabetes mellitus.

Dzivite I.,[1] Sochnevs A.,[2] Stauder G.,[3] Zeibarts M.,[4] Lauga U.,[4] Ansbergs J.[5]. 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) 1. Children’s and Teenagers’ Endocrinology Center, Bernu Kliniska University Slimnica, Pediatric University Hospital, Riga, Latvia 2. Institute of Immunology, Riga Stradins University and

Latvian Medical Academy, Riga, Latvia. 3. Riga Stradins University and Latvian Medical Academy, Riga, Latvia. 4. MUCOS-Balt Ltd., Riga, Latvia.

Summary: In this observational study, the results of a 12-month treatment of two groups of children, aged 4-18 years, with newly diagnosed type 1 diabetes were compared. Half of the patients received insulin preparation only, while the other half was treated with the combination of a similar insulin preparation and Wobenzym®. At the start of therapy, the mean values of all laboratory indices were similar in both groups of children.

A difference between mean HbA1c levels in both groups was observed at the first follow-up (p = 0.0179). During treatment, further differences became highly significant in favor of the enzyme group (p <0.0001). After 12 months, higher levels of C-peptide were found in children treated with Wobenzym® (p = 0.0012). At the start of therapy there were no differences between the groups of children in the dosage of insulin used. However, from the first follow-up visit, greater amounts of insulin were used in the control group.

The difference between circulating immune complexes (CIC) levels at the start and end of therapy was also significant in favor of the enzyme group (p = 0.0018). Enzyme therapy caused no undesirable adverse effects. Based on the results obtained, Wobenzym® can be assumed to decrease the activity of the inflammatory process and support a restitution of pancreatic b-cells. This may explain the improved metabolic compensation found in patients who received Wobenzym®. We suggest that regular intake of Wobenzym® together with individually adjusted insulin therapy can prevent the development of late pathological outcomes in diabetes.

Protease Treatment Delays Diabetes Onset in Diabetes-prone Nonobese Diabetic (NOD) Mice.

Wiest-Ladenburger U.,[1] Richter W.,[1] Moeller P.,[2] Boehm B. O.[1] Protease Treatment Delays Diabetes Onset in Diabetes-prone Nonobese Diabetic (NOD) Mice. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp. 75-78 - ISSN 0255-9625. Inter. Journal of Tissue Reactions 1997, Vol. XIX, No. 1/2, abstract 108, pp. 89 - ISSN 0250-0868 SO 112 (4-12-2) (19-04-2) 1 Abteilung Innere Medizin I, Universität Ulm, Ulm, Germany, 2 Institut für Pathologie, Universität Ulm, Ulm, Germany. 7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, May 19-21, Geneva, Switzerland

Summary: It has recently been demonstrated that proteolytic enzyme treatment modulates certain immune-mediated diseases. We have, therefore, studied the effect of administration of a protease mixture in the NOD mouse, an elegant animal model for autoimmune insulin-dependent diabetes mellitus (IDDM). Female NOD mice were fed proteolytic enzymes from age 6 weeks to 10 weeks, within the subclinical phase of IDDM. Once a week animals received intragastrically 1 mg Phlogenzym® (n=10 mice) or 0.5 mg Phlogenzym® (n=10) in 0.5 ml saline or saline only (n=10). Mice were followed for development of IDDM up to week 23. At week 21, all control animals were diabetic, whereas 25% of the treated mice were still normoglycemic at the end of the observation period.

No significant appearance of autoantibodies against either isoform of the important islet cell antigen glutamic acid decarboxylase (GAD), GAD65 and GAD67, was observed in the mouse sera as determined by a highly sensitive radioimmunoassay. The histopathological examination of pancreatic islets showed signs of insulitis in all mice with a tendency of milder insulitis in the protease-treated groups.

DIABETIC NEPHROPATHY

We know that Wobenzym® can increase levels of C-peptide in autoimmune mediated diabetes, such as type 1 diabetes. In addition to showing much insulin the pancreas can still make, C-peptide decreases the progression so the common complications of diabetes, including the **diabetic nephropathy**.

We also note that systemic enzymes can decrease the formation of “advanced glycation end products” (AGEs), which are associated with diabetic nephropathy and other complications of diabetes.

In addition, abnormal cytokines levels are normalized, including transforming growth factor beta-1 (TGF-b1), and interleukin 6.

What we have come to realize, is that the complications of diabetes are strongly mediated by the immune system. We see that controlling blood sugar with insulin is not enough to prevent complications such as **diabetic nephropathy**. The abnormal cytokine levels that occur with diabetes can safely and effectively be normalized with Wobenzym®.

Please see the *Diabetic Kidney Disease Question* in the **FREQUENTLY ASKED QUESTIONS** section on:

Kidney and Bladder Conditions & Wobenzym®

What the literature says about Wobenzym® and DIABETIC NEPHROPATHY

Enzyme Therapy in Diabetic Nephropathy – Experimental and First Clinical Data

*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) [Czech summary] * Mucos Pharma, Geretsried, Germany. ** Transplantation Institute, University Warsaw, Poland

Diabetic nephropathy is characterized by cell hypertrophy, thickening of the basement membranes and accumulation of extracellular matrix (ECM) that is attributed to an elevated protein synthesis and an inhibition of protein degradation, the latter due to reduced proteolytic activity.

The main trigger for this process is overexpression of transforming growth factor beta-1 (TGF-b1). This is induced by numerous factors such as hyperglycemia, stimulation of the RAS, formation of advanced glycation endproducts (AGE), elevated IL-6 levels, and increased mesangial stretch. A reduction of TGF-b1 levels was documented to be associated with a retardation of disease progression. Based on the findings in endothelial cells that the receptor for AGEs (RAGE) is trypsin-sensitive, the modulatory action of this serine protease was investigated in tubule cells. The distinct overexpression of TGF-b1 as well as the hypertrophy of the cells, induced by AGE-BSA, were normalized after coincubation with trypsin. In addition, the cellular accumulation of AGEs was markedly reduced. The enzyme therapy (12 mg/day of a mixture of the active ingredients of Phlogenzym®) was able to reduce the increased intraglomerular TGF-b content in rats. In a second study in uninephrectomized, STZ induced diabetes in rats the combination of Phlogenzym® with the ACE inhibitor enalapril showed an almost 67% reduction of glomerular sclerosis, while single treatment with either enalapril or Phlogenzym® led to a 20-30% reduction only, indicating clear additive effect.

In human studies (patients with rheumatoid arthritis or myelofibrosis), elevated serum levels of TGF-b were diminished by oral enzyme therapy. A clinical pilot study in patients with diabetic nephropathy demonstrated that oral enzyme therapy (2 tablets t.i.d.) is able to reduce enhanced levels of IL-6 both in serum and urine. A clinical double-blind placebo controlled pilot study on 24 patients with diabetic nephropathy, stages III or IV, was performed in 4 centers in Germany and Poland. Either the enzyme preparation Phlogenzym® or placebo was administered double-blinded for 16 weeks. 21 patients, mean age 51.3, and 53.5 years, respectively, were evaluated. Five patients in the enzyme group were suffering from diabetes type I, 5 patients from type II; in the placebo group 5 patients were suffering from the type I and 6 patients from type II. Five patients (enzyme group) had stage III nephropathy (microalbuminuria), 5 patients stage IV (macroalbuminuria); in the placebo group 4 patients had stage III, and 7 patients stage IV. At baseline, 7 patients in the enzyme group had proteinuria <1 g/day, 3 patients >1 g/day; in the placebo group 7 patients had proteinuria <1 g/day, and 4 patients >1 g/day. The groups were comparable. Blood glucose and mean blood pressure were controlled effectively.

At baseline, a proteinuria (median) of 0.4 g/day was measured in the enzyme group, 0.8 g/day in the placebo group. After 16 weeks the value was unchanged in the enzyme group (0.36 g/day), whereas it slightly deteriorated to 1.08 g/day in the placebo group ($p > 0.05$).

The albuminuria tended to lower levels (from 242.5 mg/day to 200.0 mg/day) in the enzyme group; in the placebo group, a slight increase from 508.0 mg/day to 562.0 mg/day was observed ($p > 0.05$).

Creatinine clearance did not change in either group during the 16-week treatment period (which was not at all expected in this short time), while serum creatinine tended to decline in the enzyme group (from 1.05 mg/dl at baseline to 0.95 mg/dl), and remained unchanged (at 1.2 mg/dl) in the placebo group ($p = 0.0279$).

There were recorded only 2 drug related side effects, 1 under placebo (mild diarrhea) and 1 (mild constipation) under enzyme therapy. Thus, the enzyme therapy proved to be safe.

Another double-blind, placebo controlled clinical trial with Phlogenzym® will be performed in 16 centers in Europe.

Advanced glycation end products (AGEs)-induced expression of TGF-b1 is suppressed by a protease in the tubule cell line LLC-PK1

Xiang G., Schinzel R., Simm A., Münch G., Sebekova K., Kasper M., Niwa T., Schmitz Ch. and Heidland[1] A. Advanced glycation end products (AGEs)-induced expression of TGF-b1 is suppressed by a protease in the tubule cell line LLC-PK1. Nephrol Dial Transplant 2001, Vol. 16, pp. 1562-1569. 555 KA [Czech abstract]

Abstract: Background. Advanced glycation end products (AGEs) are assumed to play a key role in diabetic nephropathy (DN). Since little is known about their action in tubule cells, we investigated in LLC-PK1 cells: (i) whether AGE-bovine serum albumin (AGE-BSA) affects cell proliferation and expression of transforming growth factor-b (TGF-b1); and (ii) whether the AGE-induced effects can be modulated by trypsin due to interference with its binding proteins at the cell surface.

Methods. Arrested cells were exposed to vehicle (control), AGE-BSA (19-76 mM) and BSA (38 mM) in the presence or absence of trypsin (0.625-5.0 mg/ml) (2.5 mg/ml) for 24 h. We evaluated cell proliferation by cell count and by [3H] thymidine incorporation, TGF-b1 expression by reverse transcription-polymerase chain reaction (RT-PCR), and TGF-b1 protein by ELISA. In addition, cell accumulation of AGEs was studied by immunohistochemical staining of the AGE imidazolone.
Results. AGE-BSA inhibited [3H] thymidine incorporation, lowered cell number and increased cell protein content as well as TGF-b1 mRNA and protein as compared with control and BSA. Immunohistochemical staining revealed a marked intracellular accumulation of the AGE imidazolone. Co-incubation of AGE-BSA with trypsin ameliorated the impaired thymidine incorporation, the decreased cell count and the enhanced cell protein content. TGF-b1 overexpression was normalized, while TGF-b1 protein declined insignificantly. Intracellular imidazolone accumulation was strikingly suppressed.
Conclusions. In the tubule cell line LLC-PK1, AGE-BSA exerts an antiproliferative effect, most probably due to TGF-b1 overproduction. The co-administration of trypsin abrogated this alteration, very likely as a result of an interaction with AGE-binding protein(s), which is supported by the decreased intracellular AGE accumulation. These findings may be the starting point for the development of specific proteolytic enzymes to interfere with the interaction between AGEs and their receptors/binding proteins.

Advanced glycation end products impair protein turnover in LLC-PK1: Amelioration by trypsin.

Xiang G., Schinzel R., Simm A., Sebekova K., Heidland A. Advanced glycation end products impair protein turnover in LLC-PK1: Amelioration by trypsin. Kidney International 2001, Vol. 59, Suppl. 78, pp. S-53-S-57. SO 130 (5-07-1) [Czech translation of abstract] Department of Internal Medicine, Institute of Physiological Chemistry, and Institute of Clinical Biochemistry and Pathobiochemistry, University of Würzburg, Würzburg, Germany; and Institute of Preventive and Clinical Medicine, Bratislava, Slovakia

Background. Advanced glycation end products (AGEs) are assumed to play a key role in the pathogenesis of diabetic nephropathy (DN) and other diabetic complications. While AGEs have been shown to exert marked effects on mesangial and endothelial cells as well as on monocytes/macrophages, little is known about their effects on tubule cells. Therefore, we addressed the questions of (1) whether AGE-bovine serum albumin (AGE-BSA) impairs the protein metabolism in the tubule cells, and if so, (2) whether the AGE-induced effects are mediated via a protease sensitive mechanism.
Methods. Arrested LLC-PK1 cells were exposed to a medium containing the vehicle (control, serum free), AGE-BSA (38 mmol/L), or BSA (38 mmol/L) in the presence or absence of trypsin (2.5 mg/mL) for 24 hours. We evaluated cell number, cell size, and cell protein content, as well as protein synthesis and protein degradation.
Results. After an incubation period of 24 hours, AGE-BSA decreased the cell number to 84.5 ± 5.5% of control and 82.5 ± 5.6% of BSA-treated cells ($P < 0.05$). [3H]-thymidine incorporation declined to 66% of control ($P < 0.05$), while BSA was without any effect. The same AGE-BSA dose reduced protein degradation ($P < 0.05$) and stimulated total protein synthesis slightly, as determined by L-[14C] Phe incorporation into acidicinsoluble proteins. These effects resulted in a rise in cell protein content (AGE-BSA vs. control, 21.9 ± 6.7%; AGE-BSA vs. BSA, 11.1 ± 6.0%, $P < 0.05$) and cell volume (AGE-BSA vs. control 9.4 ± 3.2%, AGE-BSA vs. BSA 18.4 ± 3.7%, $P < 0.05$). Coincubation with AGE-BSA and trypsin was associated with an amelioration of all investigated parameters concerning cell number, cell proliferation, raised cell protein content, decreased protein degradation, and enhanced protein synthesis.
Conclusion. These data indicate that AGE-BSA impairs cell proliferation and protein turnover in LLC-PK1 cells with a consequent rise in cell protein. Since these alterations were abrogated by coincubation with trypsin, an interference of this serine protease with the AGE-binding proteins on cell surfaces is assumed.
Keywords: diabetic nephropathy, tubule cells, protein metabolism, cell proliferation, serine protease.

Beneficial effect of proteases on TGF-beta production in glomeruli from streptozotocin induced diabetes mellitus in rats.

Paczek L.[1], Gaciong Z.[1], Bartlomiejczyk I.[1], Czyzyk A.[1], Heidland A.[2]. Beneficial effect of proteases on TGF-beta production in glomeruli from streptozotocin induced diabetes mellitus in rats. Inter. Journal of Tissue Reactions 1997, Vol. XIX, No. 1/2, pp 93, abstract 115, ISSN 0250-0868 149K/245 (19-04-2) 1. Warsaw School of Medicine, Warsaw, Poland 2. University of Wuerzburg, Germany

7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, May 19-21, Geneva, Switzerland - Abstract: Diabetic nephropathy (DM) is characterised by an excessive accumulation of extracellular matrix (ECM). In turn, perturbation of the glomeruli by the accumulation of fibronectin (FN) with high biological activity may induce both proliferation of mesangial cells and expansion of mesangial matrix. Transforming growth factor beta

(TGF-b) seems to be a key cytokine that inhibits and terminates tissue repair as well as the development of glomerulosclerosis within the kidney.
The purpose of this study was to assess TGF-b and FN accumulation in glomeruli obtained from streptozotocin induced diabetes mellitus in rats treated via intraperitoneal route daily for 21 days with 12 mg protease mixture (Phlogenzym®, Mucos Pharma, Germany). To prevent ketoacidosis, the rats were treated daily with subcutaneous injections of ultralente insulin in a dosage of 0.5 U. TGF-b and FN were measured with EIA.
The data indicate that in glomeruli from diabetic rats TGF-b production increased significantly and the treatment with Phlogenzym restores the production to the normal level. Increased accumulation of FN observed in diabetic glomeruli was significantly reduced after enzyme treatment.

ECZEMA

Eczema, also known as atopic dermatitis, is a disease characterized by chronic inflammation of the skin which is atopic, hereditary, and non-contagious.
Wobenzym® has been shown to be effective when used alone or in combination with other therapies. The research shows that some patients have a slight increase in itching for the first 4-5 days - possibly due to the speeding up and modulation of inflammatory processes and because of local microcirculation improvement.
However, in the following days the intensity of itching became rapidly decrease, so that by 15 to 18 days the intensity of skin itching became insignificant or disappeared all together, and improved skin health with decreased rash.
I should point out that eczema is often resistant to conventional therapies, and even dietary modification does not fix most cases. I suspect this is because the body is stuck in a chronic cycle of inflammation. This is why the immunomodulatory effects of Wobenzym® N are so important.
In the most resistant cases, 3 months of Wobenzym® N added to a good dietary regiment can bring improvement by arresting the inflammatory cycle. Once arrested, the improvement will continue even after discontinuation of therapy.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Skin Conditions & Wobenzym

What the literature says about Wobenzym® and Atopic Dermatitis / Atopic Eczema

Systemic enzyme therapy in the treatment of neurodermitis (atopic dermatitis) patients

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. [Russian version]

Abstract: Combined hydrolytic enzymes are used for different diseases treatment for years. Before more than 25 years M. Wolf and K. Ransberger succesfully introduced the method of systemic enzymotherapy. However, there are not publications in Russian and foreign medical sources devoted to application of the method in dermatology, in particular for neurodermitis (also known as atopic dermatitis — AtD) treatment. Because the course of many dermatosi has chronic and relapsing character and traditional basic therapy schema have not the desirable clincal effects, the new drugs and treatment methods development is of great importance. These new drugs and methods have to control successfully the course of the illnesses, preventing complications and having minimal side effects. We decided to test the therapeutical effectiveness and properties of Wobenzym® drug (the first in the line of systemic enzymotherapy drugs) at AtD patients treatment.
The study was conducted at Skin Diseases Clinic of Military Medicine Academy (Sankt-Petersburg, Russia) for 12 months as open test. There was 18 patients with AtD in the treatment groups. The patients received a monotherapy with Wobenzym® as well as combined treatment with basic treatment schema. The control group of 15 patients of similar age and clinical characteristics was formed for the clinical results evaluation and comparative analysis.
Our study demonstrated, that Wobenzym® application positively influence all the AtD manifestations and allows the more stable remission. All the patients endured the drug well.
Introduction
The Wobenzym® is known as antitumor, immunomodulative, thrombolytic and secondary analgetical agent. It is known also that systemic enzymotherapy drugs can decompose and eleminate circulating immunocomplexes, stopping by the fact the development of autoimmune diseases. It allowed to conduct a study of its therapeutical activity on AtD patients

treatment at the Skin Diseases Clinic of Military Medicine Academy (may 1997 - may 1998) with due regard to the comprehensive therapeutical principle — reliability and effectiveness with good its endurance by the patients.
The problem of AtD is still actual in dermatology due to the extent to which the dermatosis has been disseminated (from 5 to 30% in the whole spectrum of skin pathology according to the different data) and insufficient effectiveness of existing treatment methods6, 12.
It is known that AtD is a chronic dermatosis with tendencies to acute conditions at spring and autumn. Its etiology is polyfactoral, and its pathogenesis is not clear yet. At present times the opinion is often heard that the neurogen disfunctions may have secondary character.
The studies of Toropova and Sinyavskaya (1986) have shown the role of inborn genetically mediated fermentopathy of alimentary canal (AC) in children, which causes the state of manifested endogen intoxication14,15.
Ferment insufficiency of the stomach and intestine with disbacteriosis and diskinesy of gall ducts is apparent by failure of important food ingedients assimilation and by the synthesis of autoaggressive complexes of toxic and autoallergen character — circulating immune complexes (CIC). Neuroendocrine disfunctions, pathological state of the callicrein-chinine system, break of the cateholamines production and their activity occur at these conditions.
Immunodeficit state peculiar to the AtD patients is manifesting by cell and humoral immunity factors disfunction and is accompanied by reducing the whole quantity of T-lymfocytes, especially of T-suppresors, by increasing of the quantity eusinofils, by reducing of IgM and IgA levels and increasing of IgG-level, and increasing of IgE in many times. The latter is mainly caused by reagins (IgE-AT) having a leading role in development of the allergic atopic process.
Having in mind all the above mentioned and the fact that any of applied basic therapy schemes does not able to provide a stable clinical effect, we suggest that aprobation of the systemic enzymotherapy method and Wobenzym® drug may by expedient and logical.
Criteria for patients: A reliable AtD diagnosis. Different deviations in the AC functions in anamnesis. Anamnesis excluding a respiratory atopy (bronchial asthma, vasomotor cattarh).
According to B. T. Gluhenky and S. A. Grando these conditions have place at 25% of AtD patients and their treatment using ferments in form of active proteinases is inexpedient according to their studies.
Our study was 12-month open test and there was 18 AtD patients (12 men and 6 women) in the age from 15 to 62 years (an average age was 24,7 years old) In almost all the patients the illness has developed in childhood (before the 7 years old).
According to patients complaints, anamnesis study and results of examining fulfilled there was evident the alimentary disfunction in all the patients (in forms of cholecystitis, pancreatitis, gastritis, colitis with disbacteriosis etc.).
The patients were divided into two groups. The first one consisted of 6 patients (4 men and 2 women) who received monotherapy with Wobenzym; the second group included 12 patients (8 men and 4 women) who combined receiving Wobenzym® with traditionally used schemes of basic therapy. There was also a control group of 15 patients (10 men and 5 women) who received the basic AtD therapy for comparative study of the clinical study results.
All the patients from experimental groups received the drug according to the equal scheme: at first two days of treatment — 2 dragee x 3 times a day, after that — 5 dragee x 3 times a day (30-40 min. before a meal with substantial quantity of water (more than 200 ml.). The course of systemic enzymotherapy continued 1, 5-2 months depending on the time of approaching of desirable clinical effect.
As all the patients were in an acute period of the disease when symptoms are most manifestating, the time of the acute period transition to the period of stabilization and further improvement were of great interest.
The criteria of effectiveness were following:
The dynamics of local symtoms: a level of marked skin itching, lichenification, erythema, skin driedness and its turgor.
The labor data: leucocytes formula, ESR (Erythrocyte Sedimentation Rate), blood proteins, C-reacted protein, lipid metabolism state, quantity and quality evaluation of immune T- and B-cells, CIC, immunoglobulins.
We also took into account the levels of ALT and ACT for the aim of the study results evaluation.
The subjective evaluation of the treatment results by the patient using three-degree scale: “good”, “moderate manifestation” and “weak”.
A comparative analysis of the treatment results in experimental groups and in the control one taking into account the stability of the remission attained.
Results
Fig 1. [NOT AVAILABLE] Dynamics of the skin itching manifestation depending on the type of treatment
As shown on the fig.1 there was more intensive skin itching in the experimental patients groups during the first 3-4 days of treatment (in the monotherapy group — 50% of patients, in the combined therapy group — 30% of patients), however in further days the intensity of itching became rapidly decrease. Thus up on the 10th day in average the intensity of skin

itching became insignificant or disappeared at all in the group with combined treatment, on the 15th day — in the control group and on the 18th day — in the group with monotherapy.
Consequently, the systemic enzymotherapy even by the monotherapy scheme is able to reduce skin itching manifestations, and its combination with basic treatment provided an accelaration of the desirable effect to 5 days (x 1.5).
Fig 2. [NOT AVAILABLE] Dynamics of the erythema-lichenoid state manifestation depending on the type of treatment
An initial skin itching intensity increasing (short-term, during 3-4 days) could be explained by the Wobenzym's ability to stimulate inflammatory processes by activation the callicrein-chinin system and by further its transition to the settling stage.
Results (fig.2) show the durable and rather manifestated effect in the combined treatment group of patients (erythema-lichenoid skin manifestations became insignificant or practically settled in average up to the end of the 4th week, and in control group the same effect was 2 weeks later). In the Wobenzym-monotherapy group of patients the effect was also evident, but it was less manifestated. The facts are indicative, at first, that the Wobenzym® is effective even as monotreatment drug and, secondly, that additional basic AtD treatment is necessary. The latter leads to the desirable results in significantly shorter terms.
An evident confirmation of greater effectiveness of combined systemic enzymotherapy with basic AtD treatment is the fact that remission terms are significantly longer (according to our data up to 2,5-3 months in average) and the relapse duration and its manifestation is shorter. Five patients (4 men and 1 woman) which were under our examination in 6 and more months had not relapses at all. It must be also noted that 10 from 18 patients treated by Wobenzym® continued its taking (2 dragee x 3 times a day) during 3 months after our experiment as supporting preventive treatment. They are those patients who demonstrate the most prolonged time of relapse manifestation or its absence during the time of observation.
Fig.3. [NOT AVAILABLE] The subjective evaluation of the treatment applied by the patients themselves after 1 month.
Among the labor showing it must be noted reducing the total quantity leucocytes up to the normal values including eozynofils, normalization of the total blood protein level due to globulins fractions reducing, increasing of activity of T-cells immunity, reducing of the ratio T-helpers/T-supressors due to increasing of the T-supressors quantity, a reliable CIC reducing as well as IgG and IgE. The labor analysis dynamics of the patients, taking Wobenzym® combined with basic treatment, also was more manifestating.
In conclusion: The open 12-month study conducted at Skin and Venereal Diseases Clinic of Military Medicine Academy (Sankt-Petersburg, Russia) and devoted to analysis of therapeutical effectiveness of Wobenzym® drug (Mucos-Pharma, Germany) has clearly demonstarted its influence on the AtD course. As a rule the realization of the drug's treatment potential begins from the first days of the treatment applied and continues during all the time of treatment. There is not reducing of the drug effectiveness and accustomization to it eventually — on the contrary, it is evident clearly manifested increasing of the positive effect.
Applying Wobenzym® combined with traditional for the dermatosis treatment methods allows reaching better results.
Taking Wobenzym® in supporting doses (2 dragees x 3 times a day) in remission period provides more stable remission. In case of relapse its course has less manifestated character.
There were not side effects due to Wobenzym® treatment in any of patients excluding the fact that in first 4-5 days there was insignificantly increase of skin itching and more manifestated erythema in some patients. It may be explained by the drug's pharmacological properties to speed up and modulate inflammatory processes as well as by local microcirculation improvement7, 8, 10.
The results of our study support the fact that systemic enzymotherapy method (with Wobenzym) which was successfully applied in medical practice, may be also successfully applied in combined therapy of the Atd patients.
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Systemic enzyme therapy in the treatment of children with recurrent infections of respiratory tract.

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. [Czech abstract]

The article summarizes a four-year-experience with use of systemic enzyme therapy in the treatment of recurrent respiratory diseases in children.

Efficacy of Wobenzym® in the treatment of recurrent respiratory infections was studied in children treated during 1997-1999 in the pediatric and allergology and clinical immunology practice. 30 children, aged 3-15 years, showing a high sickness rate and deviation of at least one of the tested immune parameters (reduced IgA, IfM, IgG, CD3 or elevated IgE) were included into the study. The most frequent diagnoses were recurrent bronchitis (15 children), proven asthma bronchiale (6 children), and recurrent laryngitis (4 children) accompanied by rhinitis, pharyngitis, tonsillitis, and otitis. 9 children suffered additionally from atopic eczema.

Children received Wobenzym® at the daily dose of 1 coated tablet per 6 kg body weight. Daily dose was divided into 2-3 subdoses. Treatment started in autumn and lasted for 6 months. Prior to the start of Wobenzym® treatment children underwent basic laboratory examinations, smears from nose and throat, ORL examination, and screening for basic parameters of cellular and humoral immunity.

Wobenzym® treatment led to a reduction of recurrence and dyspnea attacks in patients suffering from recurrent bronchitis. Moreover, frequency of acute respiratory infections as well as number and severity of dyspnea attacks decreased also in children with proven asthma. In case of recurrent laryngitis patients there were basically no more laryngeal dyspnea attacks observed, whereas prior to the Wobenzym® treatment nearly every banal respiratory infection resulted into such attack. Even if the disease occurred, its severity was mild and administration of corticoids, so far necessary at each laryngitis attack, was not necessary anymore. In children with atopic eczema, a marked improvement of skin condition was observed and outlasted for several months after end of Wobenzym® therapy.

Before treatment, elevated levels of IgE were found in 50 % patients. Wobenzym® therapy resulted in reduction of primarily elevated IgE levels in 93 % patients. IgA level before treatment was elevated in 33 % of patients. Wobenzym® treatment led to a IgA normalization in 60 % patients. In 30 % patients IgA level increased, although it did not reach the normal values, yet. Furthermore, clinical documentation of another 109 patients treated with Wobenzym® in 1999-2001 was evaluated aiming to study the efficacy of Wobenzym® in the treatment of recurrent respiratory diseases. Study group consisted of children up to 10 years – 74 % (42 % children up to 6 years, 32 % children 6-10 years), 13 % children and youth 10-18 years, 13 % patients older than 18 years. The most frequent immunological deviations were elevation of IgE levels (41 % patients) and decreased IgA levels (20% patients).

Patients used mainly Wobenzym®, in some cases Phlogenzym. Treatment duration was 6 months. Children used Wobenzym® at the recommended dosage, usual daily dose for adults was 3x 4-5 coated tablets. Daily dose of Phlogenzym for adults was 3x2 tablets. In children, Phlogenzym was preferred in the treatment of laryngitis. Daily dose of Phlogenzym for children was 1 tablet per 10 kg body weight. Systemic enzyme therapy resulted in reduction of both frequency and severity of diseases. Therefore, associated prescription of antibiotics was also significantly reduced. Regarding the laboratory results, reduction or normalization of IgE values was found in 47 % enzyme-treated patients; lowered IgA levels

were adjusted in 64 % patients. Very interesting were the results concerning ECP (eosinophil cationic protein) – a marker of atopic inflammation. Elevated ECP levels were measured in 20 patients (20 %) before start of enzyme treatment. After the treatment, decrease of elevated ECP levels was found in 18 out of 20 patients.
Summary of findings for individual diagnoses
Recurrent tonsillitis – children repeatedly suffering from tonsillitis and using antibiotics were first treated with combination of antibiotics and Wobenzym®. If the laboratory examination performed at disease recurrence did not prove a streptococcal tonsillitis, only Wobenzym® and antipyretics were administered. Tonsillitis course was gradually palliated, frequency of disease attacks decreased and in number of patients disappeared completely.
Recurrent laryngitis – systemic enzyme therapy suppressed laryngeal dyspnea and through its immunoregulatory effect caused lowering of sickness rate. Phlogenzym was often preferred in combination with basal treatment.
Atopic eczema – positive effect of Wobenzym® was reached by a systemic effect on inflammatory process. However, an improvement of skin condition was observed after long term (3 months) treatment accompanied by further dietetic and regimen measures. Improvement outlasted after discontinuation of therapy.
Asthma bronchiale – systemic enzyme therapy was a suitable supplementary treatment, it reduced frequency of acute diseases and often enabled to reduce a dosage of inhalation corticoids.
It can be concluded that systemic enzyme therapy represents a novel therapeutic modality helping in the treatment of children showing a high sickness rate.

FIBROCYSTIC BREAST

Wobenzym® is very effective therapy for the management of fibrocystic breast disease, especially since it does not interfere with already upset hormonal balance that typically accompanies fibrocystic breast disease.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Hormone & Wobenzym®

What the literature says about Wobenzym® and Fibrocystic Breasts

Wobenzym® in therapy of various forms of fibrocystic disease with individually selected immunomodulators.

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 Research Centre of Obstetrics, Gynecology and Perinatology, Moscow, Russia. [Czech abstract]

Cancer of mammary glands is known to be registered 3-5 times more often in patients with fibrocystic disease (FCD), the risk increases 30 times as much in the signs of proliferation. We elaborated therapy regimen for patients with FCD by means of Wobenzym® having antiinflammatory, immunomodulating effect.
Immunomodulators were selected individually for every patient under the control of interferon status (IFS): Cycloferon, Ridostin, Polyoxidony. The treatment was performed in 36 women, aged from 23 to 52, having various forms of FCD: diffuse FCD: 1. multiple large filled cysts, 1.5-5.5 cm in diameter; 2. small cystic component prevailing; 3. glandular component prevailing. To assess the dynamic control of the quality of the therapy, we used radiothermometric method based on the measurement of internal temperature area (focal thermoassymetry).
Before the therapy, decreased abilities of lymphocytes to produce a -g -IFN had been noted, elevated level of serum IFN was found in blood. After the treatment, 87.3% patients had the restored ability of lymphocytes to produce a -g -IFN with the improved clinical picture, similar results were found in 23.4% of patients which underwent only basic therapy. Thus, Wobenzym® is most efficient in combination with Cycloferon in the treatment of patients with mastopathy with small cystic, fibrous and glandular component prevailing.

Enzyme therapy in treatment of mastopathy. A randomized double-blind clinical study.

Rammer E, Friedrich F. Enzyme therapy in treatment of mastopathy. A randomized double-blind clinical Study. Wien Klin Wochenschr. 1996; 108(6):180-3. Abteilung für Gynäkologic und Geburtshilfe, Allgemeines öffentliches Krankenhaus Horn. [Article in German]

In this randomized double-blind clinical study, the efficacy of an enzymepreparation (Wobenzym) was compared with hormone therapy (Lynestrenol) in 29women with mastopathy. There was a significantly greater decrease in number ofhardenings of the mammary gland after 2 months of enzyme therapy than Lynestrenoltherapy: improvement in the

former group was 100%, in the latter group 78.6%. No significant difference was observed regarding the numbers of lumps, or number andsize of cysts, sensitivity to touch, feeling of tension, spontaneous pain, and pain on pressure. The efficacy of both medicines is valued as good. Wobenzymtherapy was tolerated very well. No side effects appeared at all. Enzyme therapy is an alternative, low-risk therapy for the management of mastopathy, which does not interfere with the already upset hormonal balance of the patients.
External Link: PMID: 8650928

Treatment of fibrocystic mastopathy with hydrolytic enzymes.

F.-W. Dittmar[1], W. Luh[2]. 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. 1Department of Obstetrics and Gynecology, Starnberg District Hospital, Academic Teaching Hospital of the Ludwig-Maximilians-University Munich, D-82319 Starnberg, FRG 2Department of Gynecology, Central Hospital "Links der Weser", D-28277 Bremen, FRG

Abstract: Fibrocystic mastopathy affects about 50 % of all women in the course of their lives. Because of subjective symptoms, the risk of malignant degeneration (5 % of all cases), and ensuing physical and psychological stress, treatment of fibrocystic mastopathy is indispensable. So far, there is no causal therapy. Most common therapeutical regimens are associated with severe side effects. Therefore, the effect of treatment with an enzyme combination preparation was compared with that of placebo in a randomized double blind study in 96 patients with mastopathy over a study period of 6 weeks.
At the start of the study both groups were well comparable with respect to all relevant study parameters. At the end of the study period there were significant differences regarding the parameters of effectiveness "diameter of the largest cyst" ($p = 0.003$), "subjective disturbance by symptoms" ($p = 0.001$) and "cumulative score of complaints" ($p < 0.001$). As far as the number of cysts is concerned, there was no significant difference at the end of the study period ($p = 0.695$). Bearing in mind, however, that the initial condition was somewhat worse in the group treated with enzymes, a tendency towards better effectiveness of the enzyme combination preparation was observed with respect to this criterion, too. The difference of absolute change was significant ($p = 0.008$). The assessment of effectiveness by physician and patient showed clear advantages of the enzyme therapy over placebo.
There was a higher number of mostly mild side effects in the enzyme group, but only stomach complaints and loose stool. Since tolerance was also comparable with that of placebo, the results obtained lead to the conclusion that the enzyme combination preparation lends itself to the symptomatic treatment of fibrocystic mastopathy. Further longer-term studies, including biopsies and determination of hormonal parameters, will clarify whether causal treatment of fibrocystic mastopathy is possible.

GLOMERULONEPHRITIS

The benefits of Wobenzym® in regards to the treatment of glomerulonephritis is due to many beneficial actions of Wobenzym® including among other actions, its antioxidant effect, its anti-inflammatory functions, and its ability to restore normal lipid (fats) metabolism. One study concludes that Wobenzym® is the drug of choice, decreasing the velocity of kidney destructive processes.

Most people are familiar with the concept of "antioxidants". The reason we take antioxidants is to control the amount of oxidation that takes in cells and tissues. There must be a balance between oxidizing and antioxidazing systems in all tissues. While some oxidation is normal, excessive oxidative stress causes tissues to quit functioning properly, and can even cause cells to die. Increased oxidation is part of the inflammatory process that in glomerulonephritis. Wobenzym® has documented antioxidant properties restores the ability of the kidneys to control excessive oxidations and preserve the health and function of kidney cells and tissues.

The anti-inflammatory action of Wobenzym® spare the destruction of tissues cells and proteins, and glycoproteins, including an important protein called fibronectin. Fibronectin is a glycoprotein (a protein like molecule) that has many functions including helping cells stay anchored within the kidney, and is referred to as a "cell adhesion molecule". Since it helps maintain the structure of tissues, it is a "structural protein". In chronic glomerulonephritis the kidneys ability to make enough fibronectin to keep the kidney cells in place is impaired. Wobenzym® restores the ability of the body to make this important structural protein by controlling the excessive inflammation that interferes with normal fibronectin production and function.

One of the consequences of chronic glomerulonephritis is the development of abnormal blood lipid (fats in the blood) profiles, which cause additional damage to kidney structure and function. Wobenzym® reduced kidney tissue damage and symptoms of abnormal blood lipids. The restoration of normal lipid function has also been noted in atherosclerosis.

It is also import to remember that Wobenzym® also decreases circulating levels of anti-tissue antibodies, and circulating immune complexes (CIC), both of which are implicated in the disease processes of glomerulonephritis.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Kidney and Bladder Conditions Conditions & Wobenzym®

What the literature says about Wobenzym® and Glomerulonephritis

Antioxidant effect of Wobenzym® applied for patients with chronic glomerulonephritis

Mukhin IV. [Antioxidant effect of Wobenzym® applied for patients with chronic glomerulonephritis] [Article in Ukrainian] Lik Sprava. 2007 Jan-Mar;(1-2):58-61.

There is formation of free radicals in mesangial cells in patients with chronic glomerulonephritis which increases destruction of renal tissue and enable autoimmune inflammation. The unbalance between activity of oxidizing and antioxidazing starts developing. It accelerates the progression of the disease. The article presents the assessment of influence of enzyme medication Wobenzym® on main indices of oxidizing and antioxidazing systems. It was established the presence of antioxidant effect in Wobenzym® medication. The use of this medication in combination with other drugs and without them enables restoration of the disturbed balance.

PMID: 17684803

Systemic enzyme therapy of experimental gout glomerulonephritis

Ignatenko GA, Mukhin IV. [Systemic enzyme therapy of experimental gout glomerulonephritis] [Article in Russian] Patol Fiziol Eksp Ter. 2004 Oct-Dec;(4):26-8.

Renal lesion deteriorates the course and prognosis of gouty glomerulonephritis. Current pathogenetic therapy is not sufficiently effective. Effects of different treatments on morphological and functional manifestations of renal disorders in experimental gouty glomerulonephritis are reviewed.

PMID: 15568502 (When the MeSH Terms in PubMed are viewed, we see that Wobenzym® was used in this study.)

Experimental systemic enzyme therapy of gouty and primary glomerulonephritis

Mukhin IV, Nikolenko VIu. [Experimental systemic enzyme therapy of gouty and primary glomerulonephritis] [Article in Russian] Department of Pharmacology, Donetsk State Medical University, Prospekt Il'icha 16, 34000 Donetsk, Ukraine. Eksp Klin Farmakol. 2003 Jul-Aug;66(4):32-5.

The influence of a systemic enzymotherapy on the morphological, biochemical, and functional manifestations of the kidney damage during the experimental gouty and primary glomerulonephritis is described in comparison to the results obtained by traditional methods.
PMID: 14558349 (When the MeSH Terms in PubMed are viewed, we see that Wobenzym® was used in this study.)

Treatment of dyslipoproteinemia by systemic enzyme therapy in experimental glomerulonephritis

Mukhin IV. [Treatment of dyslipoproteinemia by systemic enzyme therapy in experimental glomerulonephritis] [Article in Russian] Patol Fiziol Eksp Ter. 2002 Oct-Dec;(4):27-8.

Patients with chronic glomerulonephritis (CG) develop disturbances of lipid blood spectrum leading to additional damage to renal structure. The existent methods of pathogenetic therapy have no effect on lipid imbalance. Recently, many autoimmune diseases have been treated with systemic enzyme therapy (SET). The authors studied SET effect in disturbed lipid metabolism in experimental glomerulonephritis. Experimental animals showed morphological and biochemical changes similar to those in CG of man. SET reduced renal tissue damage and symptoms of dyslipoproteinemia.
PMID: 12638428 (When the MeSH Terms in PubMed are viewed, we see that Wobenzym® was used in this study.)

Fibronectin content in the urine of patients with chronic glomerulonephritis as a test for the efficiency of treatment

Mukhin IV. [Fibronectin content in the urine of patients with chronic glomerulonephritis as a test for the efficiency of treatment] [Article in Russian] Klin Lab Diagn. 2001 Apr;(4):53-5.

Renal fibronectin synthesis is impaired in patients with chronic glomerulonephritis. We measured urinary fibronectin for evaluating the efficiency of various methods of treatment. Traditional therapy of patients with the nephrotic syndrome at the stage of renal failure leads to decrease of fibronectinuria, which can be indicative of the progress of nephrosclerotic process in the renal parenchyma; monotherapy with Wobenzym® during the azothemic stage of disease in patients with the urinary and nephrotic syndrome does not cause statistically significant changes in the level of urinary fibronectin, which can be regarded as inhibition of nephrosclerosis process. Hence, *Wobenzym® is the drug of choice, decreasing the velocity of nephrosclerotic processes, when pathogenetic therapy is largely limited or precluded*. Combination of wobenzyme with pathogenetic drugs in patients with the nephrotic syndrome and intact renal function suppresses fibronectinuria due to mutual potentiation of the antiinflammatory effect. Decrease of fibronectin concentration in the urine after wobenzyme monotherapy in patients with the urinary syndrome without signs of chronic renal insufficiency confirms the antiinflammatory effect of the drug.
PMID: 11393035 (When the MeSH Terms in PubMed are viewed, we see that Wobenzym® was used in this study.)

GOUT

Gout is a form of arthritis that affects mostly middle-aged men and postmenopausal women. After 3 weeks of adding Wobenzym® to conventional gout therapy, they saw an improvement of 94.1% compared to only 47.3% with only conventional therapy.
So when you look at the research, you could say that Wobenzym® is a good therapy for all forms of arthritis including osteoarthritis, rheumatoid arthritis, as well as psoriatic arthritis, juvenile chronic arthritis and even gouty arthritis.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Joint Pain & Wobenzym®

What the literature says about Wobenzym® and Gout

Systemic enzyme therapy in the gout treatment

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.

36 male patients suffering from primary gout were observed. Patients received non-steroidal antiinflammatory drugs (diclofenac sodium, movalis, phelden, and indomethacin) and allopurinol (milurit).
Patients were randomly divided into two groups:
19 patients, aged 28-69 years (mean 48.9)
17 patients, aged 29-71 (mean 50.2)
Patients in the second group received Wobenzym® (5 dragees 3 times a day for 1 week, then 4x3 dragees for 7 days, and finally 3x3 dragees for 1 month) in the complex therapy.

Before therapy and after 3 weeks, purine parameters were determined in the blood – uric acid, oxypurinol, xanthine oxidase, 5-nucleotidase, adenosine deaminase, glycine, glutamine, and aspartic acid.
The efficacy of articular syndrome treatment in patients receiving Wobenzym® reached 94.1% in comparison to 47.3% in the control group. Even more obvious were differences regarding renal syndrome.
While the conventional gout treatment led to the decrease of only uric acid and xanthine oxidase in the blood, inclusion of Wobenzym® into the therapy caused decrease of oxypurinol, 5-nucleotidase and adenosine deaminase level. Of special interest are data concerning the investigation of serum dynamic interphase tensometry before and after treatment of patients in both groups. Administration of allopurinol and non-steroidal antiinflammatory drugs evoked a suppression of surface tension in the region of short, middle, and long surface life-time. This might be caused by the accumulation of substances with surfactant properties.

HEPATITIS

Wobenzym® has demonstrable efficacy in the treatment of chronic autoimmune hepatitis (CAH) and active liver cirrhosis (LC) with a significant autoimmune process. This is in large part due to the ability of Wobenzym® to decrease the pathological effect of circulating immune complexes through its ability to remove immune complexes fixed in tissues, prevent formation of new immune complexes in tissues, help to decompose CIC, and lessen the number of CIC bound to tissues through complement system
Other mechanisms include increases cytotoxic activity of macrophages and induction of phagocytosis. Researchers concluded that that Wobenzym® appears to be an effective preparation in the treatment of patients suffering from CAH and active LC.
In toxic hepatitis, Wobenzym® has a normalizing affect on liver enzymes.
Wobenzym® produced a noticeable positive effect on immune and metabolic disorders caused by hepatitis B, with a faster tendency to recover, normalization of spleen and liver size, restoring of liver functional activity accompanied by a decrease of hyperbilirubinemia and transaminase activity were found in the test group.
In hepatitis C, the best results were found with Wobenzym® PS (Phlogenzym®) which was even superior to ribavirin and a-interferon.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Liver Conditions & Wobenzym®

What the literature says about Wobenzym® and Hepatitis

Autoimmune Hepatitis, Toxic Hepatitis, Hepatitis B, Hepatitis C: Wobenzym® in complex therapy of chronic liver diseases

Vasilenko A. M., Svec S. V. Wobenzym® in complex therapy of chronic liver diseases. State Medical Academy in Dnepropetrovsk. II National Congress of Rheumatologists in the Ukraine, Kiev, 1997

Current complex therapy of chronic liver diseases focuses on elimination of basic pathogenetic syndroms of the disease. Glucocorticoids (GC) are the most effective in the treatment of chronic autoimmune hepatitis (CAH) and active liver cirrhosis (LC) with a significant autoimmune process. They appear to be effective regulators of immune reaction which suppress antibody production. One of the undesirable side-effects of GC is formation of circulating middle size immune complexes (CIC) which intensify cytolytic syndrom (1, 2, 4). One of the main characteristics of CIC - pathogenesity - is mainly determined by the size of complexes. Pathogenesity is caused, among others factors, also by a quantitative relation between antigen and antibody. During overproduction of antibodies against any antigen or in the case of equivalent relation when antigen is fully or partially bound, large CIC are formed. Mild excess of antigen over appropriate antibody (ratio 3:2) leads to a formation of middle sized immune complexes. Insufficient antibody production causes a formation of low molecular weight complexes. Literature data (l, 2, 4) show that cytolysis is higher when middle size CIC prevail. Optimal conditions for middle size CIC formation arise in 2nd - 3rd week of the treatment by big doses of GC. Wide use of GC is limited also by risk of possible side-effects: pathological changes in organs of digestive system and kidney, insufficient anti-inflammatory effect, impossible induction of remission of the disease. All above mentioned facts speak for a necessity to search for new methods to treat chronic liver diseases. Systemic enzyme therapy seems to be one of the prospective options.

Mechanism of therapeutic efficacy of Wobenzym® in the treatment of toxic hepatitis

Korpan M.I., Korpan N.N., Tschekman I.S., Fialka V. Mechanism of therapeutic efficacy of Wobenzym® in the treatment of toxic hepatitis. National Medical University, Kiev. Dopovidi Nacionalnoi Akademii Nauk Ukrainy 1997, Vol. 9., pp. 184-187 - ISSN 1025-6415 15 KR (4-13-1)

The experimental study was held to clear up a mechanism of the treatment effect of the drug Wobenzym® in rats with toxic hepatitis, which was provoked by carbon tetrachloride. Wobenzym® in doses of 5, 20, and 100 mg/kg manifests a normalizing influence on the activity of alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and on the amounts of common and connected bilirubins in blood plasma of rats in the case of toxic hepatitis.

Pharmacological effect of Wobenzym® on the blood coagulation system.

Korpan M.I., Korpan N.N., Tschekman I.S., Fialka V. Pharmacological effect of Wobenzym® on the blood coagulation system. Likarska Sprava 1997, No. 4, pp. 70-72. [Abstract in Russian.] Pharmacology Dep., National Medical University, Kiev, Ukraine. Dep. of physiotherapy and rehabilitation, Vienna, Austria

We investigated the effect of Wobenzym® on blood clotting and fibrinolysis in the intact animals and animals with toxic hepatitis. Experiments were done with 90 Wistar rats, body weight 180-240 g.

Following parameters which characterize blood coagulation system and fibrinolysis were observed in plasma:

- time of thrombocytary plasma recalcification
- prothrombin time of thrombocyte-free plasma
- thrombin time of thrombocyte-free plasma
- fibrinolytic activity of blood

Wobenzym® dragees were ground in a mortar, dissolved in saline and administered to the rats by gastric probe at the dose of 5, 20 and 100 mg/kg in 2 ml. Control animals received the same volume of saline. To provoke a toxic hepatitis, animals were subcutaneously administered with carbon tetrachloride solution (4 ml per kg) for 4 days.

Starting at the day 5 on, animals receiving CCl4 were divided into 4 groups:

- control
- test group, receiving Wobenzym® at the dose of 5 mg per 1 kg of rat body weight. The preparation was administered using a gastric probe
- test group, receiving Wobenzym® at the dose of 20 mg per 1 kg of rat body weight
- test group, receiving Wobenzym® at the dose of 100 mg per 1 kg of rat body weight

Wobenzym® at doses of 5, 20, and 100 mg/kg showed no effect on blood coagulation and fibrinolysis after 60 min following intragastric administration.

CCl4 provoked changes in blood coagulation - prothrombin time increased by 17.2 %, time of thrombocytary plasma recalcification decreased by 10.9 % and fibrinolysis time by 28.1 %. Thrombin time did not change. Wobenzym® at doses of 5, 20 and 100 mg/kg showed normalizing effect on the above mentioned parameters in rats with toxic hepatitis.

Efficacy of systemic enzyme therapy in the treatment of patients with chronic hepatitis B

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 - ISSN 0255-9625 218 K/375 (19-05-3) Department of Therapy with Laboratory Diagnostics, Dnipropetrovsk Medical Academy, Ukraine.

Summary: To study the efficacy of systemic enzyme therapy in the treatment of patients with chronic hepatitis B virus (CHBV) in replication phase, we treated 90 patients (mean age 34.3 ± 5.3, disease duration 3.9 ± 2.1 years). Twenty-eight patients were given seven Wobenzym® tablets three times a day for 4 weeks followed by 3-4 tablets three times a day for 20 days. Thirty-two patients received parenteral interferon a2b (intron A) 5 million IU per day three times a week for 24 days. Thirty patients received Wobenzym® plus intron A simultaneously in the same dosage regimens. The group of patients receiving Wobenzym® included mainly patients in whom interferon therapy was contraindicated by dramatically expressed adverse effects and patients with intraliver cholestasis.

During the 24 weeks of therapy, clinical remission and resolution of cytolytic syndrome was achieved in 68.5% of patients administered interferon, in 62.3% of those administered Wobenzym® and in 73.5% of those administered combined therapy. Systemic enzyme therapy improved immune status parameters (increase in T-lymphocytes, normalization of T-helper/T-cytotoxic cells, decrease in the level of circulating immune complexes and immunoglobulin G) in 89% of the patients; this was similar to the immunomodulating action of interferon therapy (91 %). In 97.5% of CHBV patients, systemic enzyme therapy considerably improved the condition of the microcirculatory channel. This effect was more

highly expressed than in patients who received interferon (46%). Systemic enzyme therapy was especially efficient in patients with intraliver cholestasis.
Complete resolution was achieved in 63% of the patients and partial resolution was achieved in the remainder. In patients receiving interferon therapy, resolution of cholestasis was not observed and urosane administration was required. HbeAg/HbeAb seroconversion was observed with systemic enzyme therapy but in considerably fewer patients than in those administered interferon therapy. The positive dynamics of all the above-mentioned syndromes was expressed to a greater degree in patients receiving combined (Wobenzym®-interferon) therapy.

Influence of Wobenzym® therapy on immune and metabolic parameters in children with chronic hepatitis B

Romanova S.V., Shabunina E.I., Pereslegina I.A., Tolkacheva N.I. Influence of Wobenzym® therapy on immune and metabolic parameters in children with chronic hepatitis B. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 99-100 - ISSN 0255-9625 218 K/375 (19-05-3) Children's Gastroenterology Research Institute, Nizhni Novgorod, Russia.

Summary: We investigated the effect of the enzyme preparation Wobenzym® on immune parameters and the detoxication capacity of the liver in 20 children aged 7-14 years with chronic hepatitis B.
The control group consisted of 20 patients who received conventional basic treatment. The study group received Wobenzym® in combination with the basic treatment. The results confirmed that, compared with conventional basic therapy, complex therapy with Wobenzym® produced a noticeable positive effect on immune and metabolic disorders caused by hepatitis B in children.

Clinical use of Belosorb and Wobenzym® in the treatment of viral hepatitis B

Nikolaev V.G., Matiasch V.I., Kononenko V.V. Clinical use of Belosorb and Wobenzym® in the treatment of viral hepatitis B. Kiev, Ukraine. Presented at the conference “Current approaches in infectology, epidemiology, and microbiology”, Kiev, 1998.

20 patients with clinico-laboratory signs of progressive liver insufficiency were observed. 16 patients suffered from mid-severe and 4 with severe course of the disease. These patients were treated by a combination of Wobenzym® and Belosorb (test group). Equivalent control group was established and treated by conventional therapy.
Enterosorbent Belosorb and Wobenzym® were administered in combination – dosage 6 dragees 3 times a day (Wobenzym) and 18 tablets daily (Belosorb) – for 12-14 days. Patients received also symptomatic therapy – vitamins, allochol, karsil, glucose-salt solutions i.v.
A faster tendency to recover, normalization of spleen and liver size, restoring of liver functional activity accompanied by a decrease of hyperbilirubinemia and transaminase activity were found in the test group.
Note: Belosorb is a “highly dispersed fibrous carbon adsorbent” enterosorbent.

Oral enzyme therapy in hepatitis C patients

Stauder G., Kabil S. Oral enzyme therapy in hepatitis C patients. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp 153-158, ISSN 0255-9625 SO 112 (19-04-2) - (4-12-1) 7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, 1997, May 19-21, Geneva, Switzerland

Summary: In an open, randomized, clinical pilot trial, four groups with 20 hepatitis C patients each were treated with either 'liver support' therapy, with established medications (one group with ribavirin, one group with a-interferon), or with a novel oral test drug, Phlogenzym®, a combination of hydrolytic enzymes with the flavonoid rutosid. The liver transaminases, AST, ALT, and S-g-GT markedly improved over the period of three months in the three drug groups, but only marginally in the liver support group. The best results were found with Phlogenzym®, which was even superior to ribavirin and a-interferon. The tolerance of the oral enzymes was excellent. Further clinical trials with longer observation times, greater numbers of patients, double-blind and partly placebo-controlled, are under way.

INFERTILITY & MISCARRAIGES

Wobenzym® N has been used in the treatment of infertility for a number of reasons. First, elevated cytokines – which are frequently seen in infertility - interfere with normal function of the hypothalamic-pituitary axes. This results in altered production of pituitary hormones that are critical for fertility. So, the one benefit of Wobenzym® N is the normalization of the hypothalamic-pituitary-gonadal axis.

Another benefit would be an improvement of immunologically caused habitual miscarriages, which can be because of either autoimmune or alloimmune dysfunction. In autoimmune infertility, the miscarriage is because of autoimmune inflammation that prevents proper function of the placenta due to inflammation. In alloimmune miscarriages, the mothers' immune systema are so unstable due to abnormal inflammatory action that it actually attacks the fetus and causes the miscarriage.

The literature reveals that Wobenzym® is an effective therapy got forth autoimmune and alloimmune miscarriages. One study showed that 124 out of 144 women who had habitual immunologically caused miscarriages were able to get pregnant and give birth to 114 healthy children. Those are pretty impressive results.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Hormones & Wobenzym®

What the literature says about Wobenzym® and INFERTILITY

Immunomodulation in the treatment of reproduction disturbances

Nouza K., Madar J. Immunomodulation in the treatment of reproduction disturbances. American Journal of Reproductive Immunology 2001, Vol. 46, No. 1, pp. 106, Abst. WP8-3 541 KA Institute for the Care of Mother and Child, Prague, Czech Republic. VIII International Congress of Reproductive Immunology, Opatija, Croatia, July 2 – 6, 2001

Problem

Immune mechanisms play an important role in both male and female sterility. Even more frequent is the participation of immunity in autoimmune and alloimmune recurrent abortions. Immunopathologic reactions occur also in women suffering from preeclampsia and postclimacteric syndrome. To the important causes of female and male sterility belong chronic infections in the reproductive system.

Methods of Study

Treatment of all above mentioned disorders involved methods of immunomodulation, mainly local and systemic glucocorticoids, repeated high doses of intravenous immunoglobulines, anticoagulants (aspirin, heparin) and recently also oral enzyme therapy. In infectious processes, the rational use of antibiotics is inevitable.

Results: Immunomodulation ameliorates healing of male and female sterility, autoimmune as well as alloimmune recurrent abortions. Significant progress was also obtained in the treatment of adnexitis and prostatitis. Here, the clinical or subclinical immunological defect prompted us to use immunomodulators of chemical or biologic nature (among the latter, combination of oral animal and plant proteolytic enzymes). Their use in combination with antibiotics led to a more frequent and more effective healing not only in the infections evoked by "common" bacteria, but also in processes caused by chlamydia, mycoplasma, and ureaplasma. Conclusion: Immunomodulation represents an important part of the complex therapy of male and female sterility, recurrent abortions and chronic infections of the reproductive system.

Systemic enzyme therapy in the treatment of chronic salpingitis and infertility.

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. Institute of Pediatrics, Obstetrics, and Gynecology, Ukraine. [Ukrainian, Czech]

30 women, mean age 26.5 years, with chronic salpingitis and infertility were observed. 18 women suffered from primary infertility, 12 from secondary one. 21 patients were previously treated (antiinflammatory, hormonal therapy). 27 patients were diagnosed with unilateral salpingitis, 3 with bilateral one. Treatment started after activation of chronic inflammatory process. First, pyrogenal was administered, followed by antibacterial, anticandidous, desensibilization, and vitamin therapy. Together with antibiotics, Wobenzym® was administered at the dose of 5 dragees 3 times a day for 10 days. Patients in the control group received the same therapy without Wobenzym®.

Already after 5-6 days of Wobenzym® treatment, an improvement of patients condition was observed. Frequency and intensity of abdominal pain and in 86.4 % normalization of body temperature, appetite and intestinal function was seen. Positive changes of inflammatory signs were found after treatment - decreased infiltration, disappearance of pain on

palpation. Positive status was verified also by blood parameters: leukocyte count decreased from 8.0 ± 0.3 x 109 to 6.3 ± 0.1 x 109. Sedimentation normalized and concentration of C-reactive protein decreased under Wobenzym® treatment. Above described parameters did not change in the control group.
In 20 out of 22 patients, normalization of microflora was found. Impaired menstrual cycle normalized in 75 % patients.

Enzyme therapy - a method of immune therapy for immunologically caused habitual abortions

Dittmar, F.-W. Enzyme therapy - a method of immune therapy for immunologically caused habitual abortion. Forum Immunologie 2000, No. 3/2000, II - VIII. SO 129 (5-02-1) Gynäkologisch-geburtshilfliche Abteilung (Chefarzt: Prof. Dr. F.-W. Dittmar) des Kreiskrankenhauses Starnberg, Akademisches Lehrkrankenhaus der Ludwig-Maximilians-Universität München

Background: For patients with immunologically caused habitual abortion so far there are only few therapies possible with limited success and predominantly considerable side effects.
Objective: it was the aim of this investigation to rate the benefit of systemic enzyme therapy for pregnant women with habitual abortion in history by means of the course of pregnancy and delivery including fetal outcome. Materials and methods: 144 pregnant women with immunologically caused abortion received a gestagen preparation and an enzyme combination preparation and were observed up to delivery. The current data of pregnancy, birth and child were collected and evaluated.
Results: 114 of 144 enzyme treated pregnant women had an inconspicuous course of pregnancy up to the birth of 114 healthy children. Enzyme therapy caused no unpleasant side effects.
Conclusions: For immunologically caused habitual abortion enzyme therapy is an effective form of immune therapy. The maternal immune system is stabilized by the supplied enzymes whereby the full development of a pregnancy is easier. The further clearing of the molecular mechanisms of action is subject of current research projects. Enzyme therapy can be recommended predominantly for women, who had several abortions receiving the common forms of immune therapy without success and therefore now are looking for a therapeutical alternative. According to the previous experience enzyme therapy is very successful for women with habitual abortion with regard to completed pregnancies, and furthermore well tolerated and also cost-effective.

The use of WOBENZYM® to facilitate interferon synthesis in the treatment of chronic urogenital chlamydiosis.

Sukhikh G.T., Loginova N.S., Faizullin L.Z., Zdanov A.V, Malinina E.V, Bozedomov VA. The use of WOBENZYM® to facilitate interferon synthesis in the treatment of chronic urogenital chlamydiosis. Inter. Journal of Immunotherapy 1997, Vol. XIII, No. 3/4, pp 131-133, ISSN 0255-9625 SO 112 (19-04-2) - (5-02-2) Scientific Center of Obstetrics, Gynecology and Perinatology of the Russian Academy of Medical Sciences and the International Institute of Biological Medicine, 117815, 4 Oparin Street, Moscow, Russia. 7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, 1997, May 19-21, Geneva, Switzerland. [Czech]

Summary: Chlamydial infections are recognized as a major cause of infertility in couples and different types of pathology of male and female reproductive functions.
Female endocervical smears and male urethral swabs were examined by polymerase chain reaction (PCR) in 3,200 patients. Optimal schedule of treatment of chronic urogenital chlamydiosis using proteolytic enzymes (peroral tablet of Wobenzym®, Mucos Pharma, Geretsried, Germany) were proposed by us. In order to realize the mechanism of the therapeutic effect of proteinases we investigated the changes in the interferon system of patients. We found significant decrease of IFN a-g production and increase of serum IFN. Application of Wobenzym® led to normalization of leukocyte capability to synthesize IFN in response to all inductors. Standard antibiotic therapy led to chlamydia elimination in 61 % women and 45% men; combination of antibiotic therapy with Wobenzym® resulted in 92% cases with women and 89.5% with men, respectively. The blockade of interferon synthesis by leukocytes seems to be the cause of long-term prolongation of chlamydial infection inducing inflammation in the genital tract. Proteinases coming into the blood relieve the blockade of non-specific antibacterial defense.
Thus, proteolytic enzymes were shown as a highly efficient strengthening factor for antibiotic therapy of urogenital chlamydiosis.

Our experience with systemic enzyme therapy in the complex treatment of urogenital chlamydiosis.

Yakimova A.V., Zakharova Yu.V., Skuratov S.I., Khokhlov V.V. Our experience with systemic enzyme therapy in the complex treatment of urogenital chlamydiosis. Presented at the conference “Current approaches in diagnostics and treatment of urogenital chlamydiosis”, Novosibirsk, 1998 Medical Institute, Novosibirsk, Russia [Russian]

Presented at the conference "Current approaches in diagnostics and treatment of urogenital chlamydiosis", Novosibirsk, 1998

To increase the efficacy of chronic chlamydiosis treatment, Wobenzym® was included into the therapy. 19 women and 10 men suffering from inflammatory diseases of urinary and genital organs and/or infertility caused by Chlamydia trachomatis were observed.

All patients underwent a complex etiotropic and pathogenetic therapy. Wobenzym® was used in combination with conventional antibiotics (tarivid, rovamycin, doxycyclin). Wobenzym® was administered orally 5 dragees 3 times a day.

Complete clinical healing with elimination of Chlamydia was achieved in 79.3% patients. Rest of patients reported improved condition, although Chlamydias were still present. No Wobenzym® side-effects were seen.

KIDNEY STONES

In the most severe cases of kidney stones - patients that need surgical intervention to remove the stones – taking the systemic enzymes made them significantly less likely to get stones again.

Now what is interesting is that in those studies, the patients took enzymes for only four to five weeks – but they still had less risk of developing new kidney stones a year later!!

From what I have been able to find in the literature, I would say that by decreasing inflammation (and decreasing pro-inflammatory cytokines such as IL-6 – which is associated with kidney stone formation), and pro-Wobenzym® is able to inhibit the development of kidney stones decrease the inflammatory.

But more than that, the enzymes in Wobenzym® have proteolytic properties may decrease formation of the organic (protein) component of the kidney stone. In addition, the enzymes appear to be interacting with bikunin, a glycoprotein that is a member of the inter-alpha-trypsin inhibitor (ITI) family. Like alpha-2-macroglobulin, the ITI family of glycoproteins modulate inflammation. Proper function of bikunin decreases calcium oxylate stone formation.

We also note that patients with kidney stones complicated by pyelonephritis have very high levels of SIgA (secretory IgA) an immunoglobulin involved in local immunity of mucus membranes. This increase in the urine level of SIgA in patients with kidneys stones and pyelonephritis can play apart in the development of kidney stones. By normalizing urinary system local immunity, Wobenzym® can decreases kidney stone formation. So, there are a number of mechanisms by which Woebnzym-N can decrease kidney stone formation.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Kidney and Bladder Conditions & Wobenzym®

What the literature says about Wobenzym® and KIDNEY STONES

Coenzyme metabolic assurance of patients with recurrent nephrolithiasis in the complex treatment by systemic enzyme therapy.

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. Odessa Medical University, Department of Urology, Odessa, Ukraine. [Abstract available in Ukrainian.]

In addition to clinico-immunological investigation, the metabolic supply of enzymatic systems with pyridoxal phosphate and thiamin pyrophosphate was studied in 50 patients with recurrent nephrolithiasis complicated by chronic pyelonephritis. It was established that the value of thiamin pyrophosphate - effect was reliably increased in patients with nephrolithiasis, this witnessing the insufficient metabolic supply with coenzyme form of vitamin B1-cocarboxylase. There was a strong tendency to the growth of pyridoxal phosphate-effect. The complex treatment of patients included antiinflammatory, antibacterial therapy, as well as operative intervention in the upper urinary tract. 25 patients additionally received polyenzyme preparation Phlogenzym in the early postoperative period (for 2-3 weeks) and as out-patients (for 2 weeks more).

The complex treatment of nephrolithic patients with the use of Phlogenzym produced marked normalizing influence on the value of pyridoxal phosphate-effect which is indicative of the reduction of alterations in the urinary tract tissues. The postoperative period had a favourable course, and the control check-up carried out 12 months later revealed that the incidence of lithogeny recurrence was reliably lower than in the control group.

Immunological aspects of systemic enzyme therapy (SET) in the complex treatment of recurrent nephrolithiasis.
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. Odessa State Medical University. [Russian version]
Treatment of 50 patients suffering from nephrolithiasis, complicated by a chronic pyelonephritis in the active stage of inflammation was studied. Clinical status, urinary concretions, as well as immunological examination (E-RFC, T-helpers, T-suppressors and their ratio) and humoral immunity parameters (EAC-RFC, serum immunoglobulins, CIC) were examined. Additionally, NBT-test, phagocytary activity and index and complement system were studied.20 patients, treated by an antiinflammatory therapy and surgery, received also Phlogenzym (2 tbl. 4 times a day for 4 weeks).
After the finishing of a complex therapy patients were examined again and results were compared to those with and without Phlogenzym administration.
Patients treated by Phlogenzym showed:

- increase in total T-lymphocyte population;
- normalization of T-helpers/T-suppressors ratio;
- decreased CIC level;
- normalization of neutrophil intracellular bactericidal systems.
- Positive immunological changes correlated with a favourable dynamics of various clinical parameters: non-complicated healing of postsurgical wound;
- no chronic pyelonephritis deterioration;
- faster functional and anatomical patency of urinary tract;
- marked decrease of concretion relapses - 1-year-observation

The local immunity of the urinary system in patients with recurrent Urolithiasis

Borisov AV. The local immunity of the urinary system in patients with recurrent Urolithiasis. Lik Sprava. 1999 Apr-May; (3):111-5.

51 patients with urolithiasis complicated by pyelonephritis in the active phase of inflammation were studied for the condition of local immunity by determining the urine content of secretory immunoglobulin A (SIgA) under conditions of combined treatment with making use of phlogenzyme, a drug of II-generation systemic enzymotherapy (SE). Recordable in this patient population was a marked increase in the urine level of SIgA. Incorporation in a combined treatment of phlogenzyme results in normalizing the status of the urinary system local immunity. Evidence has been obtained on the lack of parallelism in the dynamics between the serum IgA content and urine concentration of SIgA, which fact suggests independence of local immunity. Our theory is that an appreciable increase in the urine level of SIgA in patients with urolithiasis concurrent with pyelonephritis may have an important part to play in the genesis of nephrolithiasis.
PMID: 10474953 [PubMed - indexed for MEDLINE]

LYMPHEDEMA

Lymph is the fluid that is formed from the fluids that bathe and surround the cells in the tissues of the body. This fluid is carried back to the circulation through lymphatic vessels. When these vessels do not drain properly the fluid collects in the tissues causing edema, or more specifically **lymphedema.**
So, lymphedema is the swelling of tissue due to retention of fluid in the lymph vessels. Lymphedema can have many causes, affects 175 million people worldwide, and can lead to infection, pain, severe disability and even increased risk of cancer. It is a disorder which is traditionally very difficult to treat. So you can realize why I was pleased to read the studies that were done with Wobenzym® treating lymphedema.
What I found, was that a number of studies specifically looked at the affect that Wobenzym® has on lymphedema. It was noted that there was significant reduction in pain and swelling with a lower risk of infections. Even primary lymphedema (hereditary lymphedema) showed significant improvement.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Carviovascular and Lymphatic Systems & Wobenzym®

What the literature says about Wobenzym® and LYMPHEDEMA

Diagnosis and treatment of Lymphedema

Wald M. Diagnosis and treatment of lymphedema. Interní medicína pro praxi 2003, č 8, str. 415-417.

Definition and etiology of lymphedema is briefly explained as well as stages of the disease and possible complications. Clinical finding and suitable examination methods are described. Determination of lymphedema diagnosis is schematically depicted. Medicamentous treatment using systemic enzyme therapy preparation Wobenzym® is mentioned in addition to physiotherapy.

Lymphedema.

Kafková H., Kojanová M. Lymphedema. Postgraduální medicína 2003, 5 (6), pp. 626 – 633 (Department of Dermatovenerology, 1st Medical School of Charles University, Prague)

The authors describe in detail lymphedema as an edema owing to an impaired lymph transport caused by interruption of lymphatic routes, infection or congenital abnormity. Moreover, possible complications of lymphedema, mainly development of secondary infections, are mentioned. An early and correct diagnosis using lymphoscintigraphy, ultrasound and CT examination is stressed both in primary and secondary lymphedema. Systemic enzyme therapy using combined mixtures of proteolytic enzymes (chymotrypsin, trypsin, bromelain, papain etc.) represents an effective treatment modality in pharmacotherapy of lymphedema. Enzyme therapy can improve already indurated and sclerotized tissue even in fully developed lymphedema. Based on the results of clinical trial in patients after breast cancer surgery it has been suggested that beginning of enzyme treatment immediately after surgery is an optimum therapeutic approach.

Systemic enzyme therapy and complex decongestive therapy in the patients with primary and secondary lymphedema of lower extremity

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)

Summary: The goal of this trial is the evaluation of Wobenzym® efficiency as an additional therapy to the standard treatment of lymphedema. Two groups of patients were observed: 12 women with primary lymphedema of lower extremity (group I.) and 20 women suffering by secondary lymphedema following erysipelas. The diagnosis of lymphedema was confirmed by clinical examination, duplex sonography, radionuclide lymphoscintigraphy, and by CT and MRI eventually. Complex decongestive therapy (CDT) was used as a standard treatment including manual lymph drainage, sequential gradient pneumatic therapy, a bandaging and special exercises with aquatherapy. After 4 weeks of CDT both groups were randomly divided in two halves. The subgroups I. A, II. A continue the treatment by CDT only. Subgroups I. B and II. B received Wobenzym® 3x3 tablets daily additionally to CDT. The treatment of all groups continued following 6 weeks.

During the observation subjective symptoms were estimated by questionnaire method, extremity volume differences and centripetal fraction of venous flow were measured. Serum levels of liver enzymes, creatinine and minerals were checked. In the groups receiving Wobenzym® a statistically significant amelioration of all objectives were evident comparing to groups treated by CDT only. The comparison of control visit results after 4 and 10 weeks of treatment - subjective symptoms I. B $p < 0,0004$, II. B $p < 0,0002$, extremity volumes I. B $p < 0,005$, II. B $p < 0,003$, centripetal fraction of venous flow I. B $p < 0,005$, II. B $p < 0,003$.

The treatment results in the patients with secondary lymphedema were better then the results in the patients with primary lymphedema. Nevertheless, the results of the primary lymphedema patients showed statistical significance what is remarkable in this type of lymphedema with a generally known worse curability.

Orally administered proteases in aesthetic surgery.

Dusková M, Wald M. Orally administered proteases in aesthetic surgery. Aesthetic Plast Surg. 1999 Jan-Feb;23(1):41-4.

Increasing demand for shortening the sequel period after aesthetic surgery hasled to comparative testing of optional approaches. Systemic enzyme therapy withits pharmacological effects represents a preventive and curative option forinflammatory process including healing. Excellent results were presented, namely, in the treatment of secondary lymphoedema. The incidence of hematoma, edema, and pain was followed, and the results were compared in a randomized group of 20patients with upper eyelid blepharoplasty treated with proteases (Wobenzym® drg) and in a similar group treated with systemic antiedema and hemostyptic therapy(Dicynone drg and Reparil drg). No undesirable side effects were observed. Inaddition, proteases apparently have no limitation for patients with the risk ofconcurrent cardiovascular, hepatic, or renal diseases. External Link: PMID: 10022937

Proteolytic enzymes in lymphedema therapy

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. 76 601 KA Department of Internal Medicine, City Hospital, Bardejov, Slovak Republic Department of Immunoallergology, City Hospital, Bardejov, Slovak Republic

Purpose: The goal of this study was to establish the effect of Wobenzym® in lymphedema therapy.
Material and Methods: Clinical examination, duplex sonography, radionuclide lymphoscintigraphy, CT and MRI established the diagnosis of lymphedema in 50 patients (12 primary, 38 secondary). After 4 weeks of standard treatment consisting of manual lymph drainage, bandaging, sequential gradient pneumatic therapy (Pneuven Bevuk), and special exercise therapy including aqua therapy, 25 randomly selected patients continued in standard therapy and 25 received 9 Wobenzym® tablets daily for 6 weeks. A Wobenzym® tablet contains pancreatin 100 mg, bromelain 45 mg, papain 60 mg, triacylglycerol lipase 10 mg, amylase 10 mg, trypsin 24 mg, chymotrypsin 1 mg and rutoside 50 mg. Patients had monitoring for common symptoms of pain, feelings of heaviness and decreased mobility; extremity volume changes; and, serum levels of liver enzymes, creatinine and minerals. Duplex sonography was used to determine the centripetal fraction of venous flow.
Results: Wobenzym-treated patients noted significant beneficial effects in subjective symptoms (56%, $p < 0.005$), reduction of extremity volume (55%, $p < 0.005$), duplex sonography measurements (43%, $p < 0.005$) compared with the non-Wobenzym® group.
Conclusion: Adding Wobenzym® to complete standard therapy significantly improves subjective and objective parameters of lymphedema. No adverse effects or significant changes in laboratory data were observed.

Wobenzyme and diuretic therapy in lymphedema after breast operation.

Korpan MI, Fialka V. Wobenzyme and diuretic therapy in lymphedema after breast operation. Wien Med Wochenschr. 1996;146(4):67-72; discussion 74.

The authors of this clinical study report the results of a controlled clinicaltrial in randomized parallel groups (Wobenzym® vs. diuretics) of 55 femalepatients suffering from brachial arm lymph edema subsequent to ablatio mammae. All patients received manual and machine lymph drainage as well as gymnastics as concomitant therapy. After 7 weeks of therapy the results of the volometricassessments of the arm, the circumference of the arm and the skinfold thicknessshowed significant improvements compared to diuretics. In addition, the patients receiving Wobenzym® reported a significantly higher proportion of patients free ofpain compared to the diuretics patients. Overall safety assessment results aresatisfactory thus resulting in a superior benefit/risk relation of the Wobenzym® group.
External Link: PMID: 8650941

Efficacy and tolerability of proteolytic enzymes as an anti-inflammatory agent in lymphoedema after axillary dissection due to mammary cancer

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,

Lymphoedema is a chronic disease caused by the damage of lymphatic vessels due to surgical treatment and/or radiotherapy (secondary). Another cause is the malformation or lack of lymphatic vesels (primary).
The aim of the study was to demonstrate the efficacy and tolerability of the proteolytic enzyme combination preparation Wobenzym® in additional reduction of arm volume (primary criterion) in patients with secondary lymphedema after dissection of axillary nodes due to mammary cancer. Secondary criteria were improvement of the skinfold thickness, CRP values, tension, and global judgement of the efficacy by both investigator and patient.
The study population comprised of 88 female patients aged between 30 and 80 with one-sided secondary arm lymphedema after dissection of the axillary lymph nodes (level I or II according to the St. Gallen consensus conference) due to mammary cancer, who have been treated with combined decongestive therapy. All patients received the standard treatment - a combined decongestive therapy, comprising the manual lymphatic drainage on affected sites with consecutive bandaging of the affected arm and specially designed exercises and skin care from day 1 to day 20. The test group of patients received additionally Wobenzym® at a dose of 5 coated tablets three times daily over 6.5 weeks.
Both treatment groups were well comparable. The median time between the lymph node dissection and the baseline visit was 47.5 months in the Wobenzym® group and 48 months in the placebo group.

For measuring the indicator volume reduction in arm lymphedema, a Volometer was used. For the indicator tension, a four-point rating scale was used. All the measurements were carried out on days 1, 9, 19, and 45 (final visit). CRP value was measured on days 1 and 19.
On the ill arm both groups showed a decrease of volume until visit 4 (day 45).
Both groups showed an almost identical course of the volumetric development between baseline visit and final end point visit, although there was a slight superiority of Wobenzym® for the development between visit 3 and 4 with regard to the percent changes of –5% and more without statistical significance.
Both groups showed the greatest decrease of skinfold thickness between visits 2 and 3 with a very similar development between baseline visit and final visit with regard to the results of the ill arm. The results of the percent changes from baseline with regard to visit 2, 3, and 4 showed a mean reduction by –29.84% for the verum group and –15.73% for placebo group. The development between visit 3 and 4 showed only slight superiority for the verum group.
Both groups showed an almost similar decrease of tension in the ill arm until visit 4. A percent change of 100 % (total improvement) was reached by 62.79 % patients in the Wobenzym® group and by 47.62 % patients in the placebo group. The percent changes between visits 3 and 4 – time where no concomitant combined decongestive therapy was applied – showed a clear superiority of the Wobenzym® treated patients.
CRP was measured at visit 1 (baseline) and 3 (day 19). Wobenzym® group showed better results than placebo group with regard to the CRP development between baseline visit and visit 3: out of 15 patients with high baseline findings five patients normalized in the Wobenzym® group.
Out of 13 patients with high baseline findings in the placebo group, only one patient normalized. For patients with high CRP-values at baseline there has been mean percent change from baseline of –39.8%, while in the placebo group –17.4%. There was a clear superiority for the verum group with regard to the CRP development between visit 1 and 3.
Overall, 15 adverse events were recorded, 7 for the verum group and 8 for the placebo group. The adverse events in the verum group were all gastrointestinal complaints of moderate intensity and rated as possibly (6 cases) or definitely (1 case) related to the study medication. All the patients showing adverse events completely recovered without sequelae.
All in all, the study failed to demonstrate efficacy in edema-related criteria (most likely due to extensive concomitant physical therapy in all patients) but demonstrated efficacy of Wobenzym® with regard to the inflammation-related criteria. The inflammation-related criteria showed more than small superiority of Wobenzym®. Moreover, for the subgroup “no chemotherapy” the inflammation-related criteria showed more than medium-sized superiority of Wobenzym®. Reduced inflammatory tissue conditions are the basis for minimizing fibrosis thus preventing further inflammation and infection.

MULTIPLE SCLEROSIS

Multiple sclerosis patients treated with Wobenzym® showed a decreased number of attacks and a shortened duration of those fewer attacks that did occur. The studies conclude that the stabilization of the nervous system and the improved activities of daily living were a direct result of the decreased inflammatory activity due to use of Wobenzym®.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Use of Wobenzym® for Treating Diseases of Brain & Nervous System

What the literature says about Wobenzym® and MULTIPLE SCLEROSIS

Use of oral enzymes in multiple sclerosis patients.

Mertin J.[1], Stauder G.[2], ESEMS working group[3]. Use of oral enzymes in multiple sclerosis patients. Inter. Journal of Tissue Reactions 1997, Vol. XIX, No.1/2, pp 95 1 Neurological Rehabilitation Centre Kiliani, D-91438 Bad Windsheim, Germany 2 Mucos Pharma, Clinical Research, Malvenweg 2, D-82538 Geretsried, Germany 3 European Study on Enzyme Therapy in Multiple Sclerosis 7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, May 19-21, Geneva, Switzerland

Abstract: In 1986, a first report on a cohort of 300 multiple sclerosis (MS) patients treated with hydrolytic enzymes describes stabilizing of the disease and reduction of the relapse rate. These findings have been supported by case reports and by subjective patient reports. Soon it became clear that a stepwise approach was necessary, in order to prove whether oral enzymes are effective and safe in MS. As first step an open multicentric study was performed. An evaluation of the data showed hydrolytic enzymes to stabilize the neurological impairment and to improve activities of daily living. Now a randomized, prospective, double-blind, placebo-controlled study according to the European GCP-guidelines is going on. 300 patients from 23 European centres are included to randomly receive Phlogenzym or placebo in a daily dose of 3 tablets

b.i.d. or 2 tablets t.i.d. over a period of 2 years. Progression rate, relapse rate, neurological signs and symptoms (incl. MRI), emotional status and unwanted side effects are main endpoints. Some have already finished the treatment period. Results of that study will be available in early 1999. In case the enzymes prove to be superior over placebo a safe and inexpensive therapy in the management of MS would be available.

Wobenzym® and Wobe-Mugos® in the Treatment of Multiple Sclerosis.

Hana Krejcová. Wobenzym® and Wobe-Mugos® in the Treatment of Multiple Sclerosis. PharmaScript, Kathi-Kobus-Steig 1, D-82515 Wolfratshausen, Germany

Summary: In this open randomised clinical phase III trial (acc. to German Drug Law) with two parallel groups, efficacy and tolerance of two enzyme drugs were tested in patients with multiple sclerosis: during acute attacks, Wobenzym® tablets (high dose) and Wobe-Mugos® ampoules were used, in the interval low dose Wobenzym® tablets. This was compared with a treatment with ACTH/corticosteroids during attacks and - in patients with worse prognosis and in advanced stages if necessary cyclophosphamid in the interval.

40 patients with established multiple sclerosis (clinical follow-up, liquor diagnosis, MRI, CT and/or VEP, optional SPECT) were taken into this study. 20 patients received the enzyme preparations and 20 ACTH/corticosteroids. The data of all patients were evaluable.

The study was conducted under the direction of Prof. MUDr. Hana Krejcová, DrSc., Neurologická klinika, Pediatrická Fakulta, Universita Karlova, FN Motol, V úvalu 84, 15012 Praha 5, Czech Republic.

In any case the therapy in the enzyme group started with high dose enzymes: During the first week the patients received 1 ampoule Wobe-Mugos® pro inj. and 30 tablets of Wobenzym® daily. In the second week the patients got 1 ampoule Wobe-Mugos® every other day and 30 tablets of Wobenzym® daily. From the third week the patients received a maintenance dose of 9 tablets Wobenzym® each day.

The patients in the comparative group received throughout an attack either a pulsed therapy of high dose corticosteroids (3 days 1000 mg/die methylprednisolone i.v., 2 days' pause, 3 days tapering off), an oral therapy with corticosteroids (60 - 80 mg/die methylprednisolone orally 2 to 4 weeks, last week tapering off) or a therapy with ACTH (100 1.E. ACTH daily during 2 weeks, last week tapering off). During intervals patients with worse prognosis and/or advanced stages got daily if necessary 3 mg/kg body weight oral cyclophosphamide. Patients with good prognosis and in early stage received no interval therapy.

The patients were comparable at baseline with regard to age, sex, family case history, classification of multiple sclerosis by Poser, kind of disease, parameters of the functional system, of the performance system and of the social environment (Wilcoxon-Mann-Whitney- U-Test: $p > .05$).

The main endpoint for statistical evaluation was the extended Kurtzke disability scale (EDSS).

Despite randomisation, the patients had a significantly different mean value at baseline (enzyme group: 3.3 - corticosteroid group: 4.5 - $p = .015$). After adjusting the baseline values of either group to 100%, a statistically significant difference in favor of the enzymes was demonstrated from the sixth month ($p < .01$), an even highly significant difference at end of therapy ($p < .001$).

If the difference at baseline is judged as clinically so relevant that a direct comparison during the course of the therapy is not acceptable, there is nevertheless a difference in favor of the enzymes in the change of the Kurtzke scale: whereas the value improved until the last available value in the enzyme group by 24.2% (from 3.3 to 2.5), it worsened in the corticosteroid group by (-) 2.2% from 4.5 to 4.6.

As secondary criteria the parameters of the functional system, of the performance system and of the social environment, the serodiagnosis, the diagnosis of the liquor, and the subjective judgement of efficacy and tolerance were evaluated statistically.

The parameters of the functional system (the findings of the pyramidal tract, cerebellum, sensorium, vesicorectal function, index of the gait pattern, sum score), of the performance system (dress and undress, personal hygiene, fatigability,) and of the social environment (work, sumscore) showed statistically significant ($p < .05$) differences at end of therapy in favor of the enzymes. The data of the parameter"walking" and of the parameters of the social envorinment showed significant advantages in the corticosteroid group.

There were other statistically significant differences in favor of the enzyme treatment for the number of hospitalisation and for the number and duration of multiple sclerosis attacks: there was a total of 15 hospitalisations necessary in the enzyme group (mean 0.8 hospitalisations per patient) and 35 hospitalisations in the corticosteroid group (mean 1.8 - $p = .038$). The mean duration of hospitalisation (enzymes: 25.7 days, corticosteroids: 60.7 days) just missed significance ($p = .055$). 15 attacks were documented in the enzyme group (mean 0.8 attacks per patient) with a mean duration of 28.7 days, 37 attacks

in the corticosteroid group (mean 1.9 - p - .019) with a mean duration of 58.2 days (p = .02). There were no differences in progression and severity of the attacks between the groups (p > .05).
The result of the therapy was judged by the physician and by the patients at end of therapy as 3.1 ("slight improvement") in the enzyme group and as 4.1 ("unchanged") in the corticosteroid group. The groups differed statistically significantly in favor of the enzyme treatment (p < .05).
The judgement of efficacy by the physician was 2.0 ("good') and by the patients 2.1 ("good") in the enzyme treated group and 3.1 ("moderate") in the corticosteroid group. The difference was statistically significant in favor of the enzymes (p < .05). The tolerance of the treatment was judged by the physician and by the patients as 1.4 ("very good" to "good") in either group. The duration of treatment was comparable in both groups. The average duration was 19.4 months in the enzyme group and 23.0 months in the corticosteroid group. The difference was not significant (p > .05).
Three "moderate" adverse events in two patients (gastro-intestinal symptoms and cholecystitis, transient increase of transaminases) were documented in the enzyme group. The gastro-intestinal symptoms started during the 12th month, the cholecystitis during the 15th month, but they were "certainly not" caused by the enzymes. The increase of transaminases started during the tenth month. As there was not found any causa, the relationship to the enzyme therapy was judged as "probably". The enzymes were discontinued in the first patient after the second adverse event, in the second patient immediately. No sequelae were documented.
There were no adverse events noted in the corticosteroid group. The difference was not significant (p = .605).

Use of oral enzymes in multiple sclerosis: phenotyping of peripheral blood lymphocytes from MS patients under long-term treatment with orally administered hydrolytic enzymes.

Stauder G.,[1] Donnerstag B.,[2] Baumhackl U.,[3] Buschmans E.[1]. 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, ISSN 0255-9625 SO 112 (19-04-2) - (18-00-2)

1Mucos Pharma, Clinical Research, Geretsried, Germany, 2Dept. of Biological Chemistry, University Medical Center, Frankfurt/Main, Germany, 3Dept. of Neurology, District Hospital, St. Pölten, Austria. 7th Interscience World Conference on Inflammation, Antirheumatics, Analgesics, Immunomodulators, 1997, May 19-21, Geneva, Switzerland -

Summary: Oral hydrolytic enzymes in combination with rutosid have been applied in MS patients for more than 20 years. We investigated whether immunological alterations in MS patients are influenced by enzyme treatment. We determined the phenotypes of specific lymphocytic antigens in 12 patients with relapsing-remitting MS, who were known to be under long-term treatment with oral hydrolytic enzymes (Phlogenzym®). Matched untreated (i.e., only treated for symptoms) MS patients (n=18) and healthy volunteers (n=10) served as controls.
For phenotyping, the following lymphocytic antigens were measured: CD4, CD8, CD3, CD2, CDl9, CD56, CDl4, CD45, CD45RA, CD45RO, CD25, CD54 and HLA-DR. Tests were carried out with a panel of different fluorescence-conjugated murine monoclonal antibodies and subsequent two color flow-cytometry. Data is expressed as percentage gated cells. Symptomatically treated patients had increased CD4, CD19, CD2 and CD45RO, CD54 and CD56. These changes were influenced by hydrolytic enzymes in the following manner: CD8 was markedly decreased; CD4, CD2, CD25, CD-45-RO, CD-45RA, CD56 slightly decreased. Furthermore, a statistically significant decrease was found for CD45 and CD54. From these results the conclusion can be drawn that positive clinical findings in MS patients under oral hydrolytic enzymes are causatively linked to a decrease in inflammatory activity.

MYOCARDIAL INFRACTION

Patients who have suffered a **myocardial infarction** – a heart attack – had lower risk of re-infarction when they were given Wobenzym®. Normalization of lymphocytes, and a **lowering of circulating immune complexes** was observed.
A parallel study of myocardial infarction patients and two groups of rabbits reported a "significant decrease of cholesterol level" in both the clinical and the experimental studies. They concluded that "it can be recommended to use Wobenzym® in complex treatment of myocardial infarction patients to reduce risk factors of reinfarction."

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Cardiovascular and Lymphatic Systems & Wobenzym®

What the literature says about Wobenzym® and MYOCARDIAL INFARCTION

Systemic enzyme therapy in the treatment of patients with myocardial infarction.

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. 11 KR [Czech translation of abstract]

An immune statute of myocardial infarction (MI) patients is significantly impaired. Preparation Wobenzym® (Mucos Pharma, Germany) shows a hypolipidemic and immunonormalizing effect, although its applicationh in the treatment of MI patients has not been studied yet.
Two groups of patients with hyperlipidemia was administered with Wobenzym: A (30 patients - 9 coated tablets for 10 days) B (13 patients - 9 coated tablets for 30 days). Patients received also beta blockers, nitrates and aspirin.
Controlled parameters were: level of cholesterol, triglycerides, HDL, LDL and VLDL, coefficient of atherogenity, lipoprotein level, activity – concentration of diene conjugates, malonic acid dialdehyd, catalase activity. Parameters of cell and humoral imunity –count of monocytes, neutrophil granulocytes, phagocytary activity, level of imunoglobulins, circulation immune complexes, antibodies against infarcted myocardium, monoclonal antibodies – were followed, too.
In parallel with this clinical study an animal experiment was conducted on two groups of rabbits with alimentary hypercholesterolemia. First group of animals was control, second group received Wobenzym® in the daily dose 3 times higher than the calculated dose per 1 kg of patients` body weight. Following parameters were controlled during 2, 4, 6 and 8 weeks: level of cholesterol in plasma, catalase activity, malonic acid dialdehyd, coefficient of atherogenity, monocyte count.
Lowering of cholesterol level by 12% and lipoproteins by 16% was observed in the patients from first group already after 10 days, whereas patients from the second group showed decrease of cholesterol level by 24% and lipoproteins by 31% within one month. Level of malonic acid dialdehyde showed no changes for 10 days, after one month was lowered.
These results support an antiatherogenic effect of Wobenzym® which can be seen after 10 days and antioxidant effect which can be seen after long-term treatment.
In 2/3 of MI patients a lowered level of B and T lymphocytes and T helpers and in 1/2 of patients lowering of T suppressors and natural killers were found. Within one month the activity of cellular imunity increased (normalization of T helper and natural killer level). An elevated level of circulating imune complexes was found in 80% of patients from both groups. Wobenzym® therapy led to the decrease of immune complex level by 38% in 88% of patients in second group.
Additionally, in all patients a higher titer of antibodies against infarcted myocardium was observed. Antibody titer decreased from 16 to 9 units in 50 % of patients in the second group after Wobenzym® therapy.
Antiatherogenic and hypolipidemic effect of Wobenzym® was experimentally verified. Treated animals showed cholesterol level nearly two times lower than animals in control group. In treated animals a decreased activity of oxidative reactions and increased activity of antioxidative enzymes (seen in the level of malonic acid dialdehyde) was observed. In the group of treated animals an increased catalase activity was measured.
Obtained results support a therapeutical effect of Wobenzym® in the complex pathogenetic treatment of patients with myocardial infarction.
Immunonormalizing, antiatherogenic and antioxidative effects of Wobenzym® influence the risk of reinfarction.
Investigation of the effect of long-term Wobenzym® treatment on MI patients is planed.

Systemic enzyme treatment as a method of secondary prevention in patients after myocardial infarction in the rehabilitation period.

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) Ukrainian Institute of Cardiology,"Ukrprofzdravniza", Kiyev, Ukraine

Abstract: Despite its proved hypolipidemic and immunocorrective effects, Wobenzym® ("Mucos Pharma" Germany) has not been used in patients with myocardial infarction (MI) in period of rehabilitations.

The aim of this study was the estimation of influence treatment with Wobenzym® on lipids parameters, antioxidant activity and immunological indices in patients after myocardial infarction.

30 myocardial infarction patients in 3rd-4th week of the disease were treated with Wobenzym®. The patients also received beta-adrenoblockers, nitrates, aspirin and inhibitors ACE.

Parallel experimental studies with two rabbit groups with a hypercholesterolemia model were carried out. Cholesterol content in plasma, blood pro- and antioxidant parameters and state of blood monocytes were estimated.

Evident hypolipidemic effects (significant decrease of cholesterol level) and immunocorrecting effects (significant decrease of titer of antibodies to the infarcted myocardium and circulating immune complexes) of Wobenzym® were demonstrated in clinical and experimental study.

Based on obtained results it can be recommended to use Wobenzym® in complex treatment of myocardial infarction patients to reduce risk factors of reinfarction.

New approaches to modern cardiology based on systemic enzyme therapy.

Kovalenko V.N., Sledzevskaya I.K., Ryabokon E.N., Gavrilenko T.I., Terzov A.I. N.D. New approaches to modern cardiology based on systemic enzyme therapy. Int. J. Immunotherapy 2001, Vol. XVII, No. 2/3/4, pp. 101-111 - ISSN 0255-9625 218 K/375 (17-10-3)- (19-05-3) Strazhesko Institute of Cardiology, Academy of Medical Sciences, Ukraine.

Summary: Enzyme therapy is a modern medical method based on the complex action of targeted mixtures of hydrolytic enzymes on the main pathological processes by nonspecific and specific immune mechanisms. The efficiency of enzyme therapy is supported by studies performed by a group of Ukrainian doctors on the treatment of postmyocardial infarction patients that led to normalization of cholesterol levels. In these studies, the treatment consisted of Wobenzym®.

Under the influence of this drug, some of the immune parameters in patients with postmyocardial infarction returned to normal. Nevertheless, many factors of immune inflammation in postmyocardial infarction patients have not yet been researched and the principles of assignment of enzyme therapy during rehabilitation have not been developed. Immune inflammation in postmyocardial infarction patients was investigated and the research concentrated on the influence of enzymes on immune factors during rehabilitation.

Seventy-three patients with postmyocardial infarction were divided into two groups: group 1 consisted of 52 patients treated with Wobenzym® for 6 months and group 2 consisted of 21 patients given basic therapy (aspirin, b-blockers and nitrates) only. Material for research was venous blood, which was taken in the morning prior to the beginning of Wobenzym® therapy and again after 1, 3 and 6 months of treatment. Biochemical research included tracing of cholesterol, triglycerides and atherogenic potential.

Immunology research included study of the factors of immunity, cytokine levels and immunoinflammatory reaction. Postmyocardial infarction patients showed changes in lipid, immunological and circulatory dynamics. This study concentrated on analyzing the influence of enzyme therapy on changes in lipid, immunological and circulatory dynamics and determination of the efficiency of its extended application. A set of major parameters that are important in myocardial infarction are described.

It was found that inclusion of Wobenzym® in the complex treatment of postmyocardial infarction patients is beneficial, as this drug has immuno- and lipid correction effects. Systemic enzyme therapy helps to improve the patient's biochemical and immune abnormalities.

OSTEOARTHRITIS

Considering patients with **osteoarthritis**, also known as degenerative joint disease: A 2006 six-week phase III, randomized, double blind, parallel group study compared systemic enzyme support with diclofenac the generic name for a nonsteroidal anti-inflammatory drug that is widely used to treat arthritis. Keep in mind that diclofenac can increase the risk of life-threatening heart or circulation problems, including heart attack or stroke – and the longer it is used, the greater the risk. **Contrast** that to those studies that conclude that Wobenzym® reduced the risk if myocardial infarction. Now, consider this: the 2006 study found systemic enzymes were as effective as diclofenac – and noted that the systemic enzymes were better tolerated.

A 2004 randomized, double-blind, parallel group trial by a different group of researchers came to the same conclusion. Within the six-week observation period, they noted that that systemic enzyme support "can be considered as an effective and safe alternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee."

And before that, a 2001 randomized, controlled, single-blind study of seven weeks' duration found that systemic enzyme support "is as efficacious and well tolerated as diclofenac" in the management of active osteoarthritis.

A number of studies conclude that Wobenzym® is an effective and safe alternative to NSAIDS in the treatment of painful episodes of **osteoarthritis** of the knee and hip[47-49].

So, we see that systemic enzyme support is as effective as – and in my opinion safer than - nonsteroidal anti-inflammatory drugs for the management of osteoarthritis. We see similar results for rheumatoid arthritis and other forms of arthritis.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Joint Pain & Wobenzym®

What the literature says about Wobenzym® and OSTEOARTHRITIS

Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee--a double-blind prospective randomized study.

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.

The aim of this study was to compare the efficacy and safety of an oralenzyme-rutosid combination (ERC) containing rutosid and the enzymes bromelain andtrypsin, with that of diclofenac in patients with osteoarthritis (OA) of theknee. A total of 103 patients presenting with painful episodes of OA of the knee were treated for 6 weeks in two study centers in a randomized, double-blind, parallel group trial. Altogether, 52 patients were treated in the ERC group and51 patients were treated in the diclofenac group. Primary efficacy criteria were Lequesne's Algofunctional Index (LFI) and a 'complaint index', including pain at rest, pain on motion and restricted function. The efficacy criteria were analyzedby applying the Wilcoxon-Mann-Whitney test that provides the Mann-Whitneyestimator (MW) as a measure of relevance. Non-inferiority was considered to beproven if the lower bound of the 97.5% one-sided confidence interval (CI-LB) was higher than MW = 0.36 (benchmark of not yet relevant inferiority). Bothtreatments resulted in clear improvements. Within the 6-week observation period, the mean value of the LFI decreased from 13.0 to 9.4 in the ERC group and from12.5 to 9.4 in the diclofenac group. Non-inferiority of ERC was demonstrated byboth primary criteria, LFI (MW = 0.5305; CI-LB = 0.4171) and complaint index (MW = 0.5434; CI-LB = 0.4296). Considerable improvements were also seen in secondary efficacy criteria, with a slight tendency towards superiority of ERC. The global judgment of efficacy by physician resulted in at least good ratings for 51.4% of the ERC patients, and for 37.2% of the diclofenac patients. In the majority ofpatients tolerability was judged in both drug groups as very good or as good. Thecurrent study indicates that ERC can be considered as an effective and safealternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee. Placebo-controlled studies are now needed to confirm theseresults.

External Link: PMID: 15278753

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.

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.

OBJECTIVE: The objective of this study was to establish the non-inferiority of anoral enzyme therapy (Phlogenzym-(PE)) as compared to the non-steroidalanti-inflammatory drug (NSAID) diclofenac (DC) in patients with osteoarthritis (OA) of the

hip. METHODS: Ninety patients presenting with painful episodes of OA of the hip were treated for 6 weeks in one study centre in a phase III, randomised, double blind, and parallel group trial. Altogether, 45 patients weretreated in the PE group and 45 patients were treated in the DC group. Primaryefficacy criteria were: WOMAC dimensions pain, joint stiffness and function, and Lequesne index as multiple endpoint according to O'Brien. The efficacy criteriawere analysed applying the test of non-inferiority with regard to mean changesand frequencies, t-test, U test, ANCOVA and descriptive methods.
RESULTS: Within the 6 weeks' observation period, the adjusted changes from baseline to endpoint ofthe target parameters worked out as follows (adjusted differences, mean +/- SEM): WOMAC subscale pain (PE -10.3 +/- 1.2, DC -9.5 +/- 1.2), WOMAC subscale jointstiffness (PE -3.9 +/- 0.5, DC -3.6 +/- 0.5), WOMAC subscale physical function (PE -31.7 +/- 3.5, DC -29.7 +/- 3.5), Lequesne's index (PE -2.89 +/- 0.47, DC-2.27 +/- 0.47). Non-inferiority of PE as compared to DC with regard to theO'Brien's global sum of the standardised adjusted changes from baseline toendpoint in pain, stiffness, physical function, and Lequesne's index wasestablished with p = 0.0025. PE was simultaneously non-inferior as compared to DCwith regard to the 4 single endpoints: WOMAC subscale pain (p = 0.0033), WOMACsubscale joint stiffness (p = 0.0061), WOMAC subscale physical function (p =0.0039), Lequesne's index (p = 0.0008) (closed test procedure). The equivalencetests remained insignificant due to comparatively lower effects of DC. For 71.1% of the PE patients and for 61.4% of the DC patients rates of good or very goodglobal investigator assessments of efficacy were calculated (test ofnon-inferiority: p = 0.0011). In the majority of patients, tolerability wasjudged in both drug groups as very good or good.
CONCLUSION: This trial showedsignificant non-inferiority from 6 weeks' treatment with PE in patients with OA ofthe hip with regard to the WOMAC dimensions pain, stiffness and physicalfunction, to Lequesne's index, to the investigator and patients assessments ofefficacy, and to the responder rates based on pain, physical function, andpatient assessment of efficacy. With regard to drug tolerability some tendencies in favour of PE were detected. However, in this study there was no realdifference between PE and DC 100 mg/day, implying an equal benefit-risk relation between the substances. PE may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level.
External Link: PMID: 16539815

Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthrosis of knee joint: an open randomized controlled clinical trial.

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.

OBJECTIVE: To compare the efficacy and tolerability of an oral enzyme preparation (Phlogenzym®) with that of an NSAID (diclofenac) in the treatment of activeosteoarthrosis. METHODS: Prospective, randomized, controlled, single-blind study of seven weeks' duration at a tertiary care centre wherein 50 patients aged 40-75 years, with activated osteoarthrosis of knee joint were randomized to receive phlogenzym tablets (2-3 tablets, bid) or diclofenac sodium 50 mg bid for threeweeks. RESULTS: At the end of therapy (three weeks) and at follow-up visit atseven weeks there was reduction in pain and joint tenderness and swelling in bothgroups, and slight improvement in the range of movement in the study group. Thereduction in joint tenderness was greater ($p < 0.05$) in the study group receiving phlogenzym. CONCLUSION: Phlogenzym is as efficacious and well tolerated asdiclofenac sodium in the management of active osteoarthrosis over three weeks of treatment.
External Link: PMID: 11584936

PELVIC INFLAMMATORY DISEASE

Quite a few conditions are improved by adding Wobenzym® to the treatment plan. We see it used with various forms of both acute and chronic pelvic inflammatory disease. It is a very effective therapy since it does not not cause hormonal imbalance, but addresses the inflammatory condition.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Hormones & Wobenzym®

What the literature says about Wobenzym® and PELVIC INFLAMMATORY DISEASE

Adnexitis, Salpingitis, Salpingoophoritis, Oophoritis
Wobenzym® in the Treatment of Chronic Pelvic Inflammatory Disease.

Friedrich F. Wobenzym® in the Treatment of Chronic Pelvic Inflammatory Disease. Germany Report provides through: PHARMASCRIPT, Kathi-Kobus-Steig 1, W-8190. Study Number: MU-89210.

Summary: This study was carried out as a randomised, double blind clinical trial with parallel groups and active control. The aim was to prove, whether efficacy and tolerance of WOBENZYM® are comparable to Diclofenac in patients with chronic pelvic inflammatory disease (PID).
44 female patients with anamnestically and laparoscopically verified chronic PID were taken into this study. The data of 40 patients were evaluable.
The study was carried out by Univ. Prof. Prim. Florian Friedrich, M.D., City Hospital, Spitalgasse 10, A-3580 Horn, Austria.
The patients of the enzyme group were given 5 enteric coated tablets WOBENZYM® and 2 capsules placebo t.i.d., the patients of the Diclofenac group 5 tablets placebo and 2 capsules with 50 mg Diclofenac each t.i.d. ("double dummy" method). The drugs were randomised and blinded. Duration of therapy was 3 weeks. At start of the trial the patients were comparable with response to age, height, weight, pain on motion, pain under pressure, abdominal defence, abdominal pain, micturition difficulties and painful defecation.
Main criterion for statistical evaluation was a sum score computed from the symptoms gynecological palpation (pain under motion, pain under pressure, abdominal defence), ESR score and WBC score at end of therapy.
Secondary criteria were the objective and subjective variables according to the CRF like general condition (abdominal pain, micturition difficulties, painful defecation) and C-reactive protein. The statistical tests were calculated on equivalence between both treatment groups.
There was no statistical difference between the both groups after 3 weeks of therapy in the main and secondary criteria ($p > 0,05$).
The physician judged the efficacy of the therapy after three weeks in the enzyme group as 1.9 ("good") and in the Diclofenac group as 1.6 ("good"); the judgement of the patients was 2.0 ("good") in each group. The tolerance of the tested drugs was judged by the physician as 1.9 ("good") in the enzyme group and as 1.7 ("good") in the Diclofenac group, by the patients as 2.1 ("good") in the enzyme group and as 1.8 ("good") in the Diclofenac group. Adverse events were documented in three patients (13.6%) of the Diclofenac group only. Two of the adverse events were gastro-intestinal comp1aints, in one case a blepharedema was documented. The onset was between the 1st and the 8th day of therapy and the mean duration was 7.3 days. Severity of the adverse events was 2.0 ("moderate") on average.

Therapy of adnexitis - enhancement of the basic antibiotic therapy with hydrolytic enzymes.

Dittmar F.-W.[1], Weissenbacher E. R.[2]. 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. WE 12 (5-03-2) = WE 44 (5-04-2) nìm. [Czech]*1 Department of Obstetrics and Gynecology, District Hospital Starnberg, Teaching Hospital of the Ludwig-Maximilians-University Munich, W-8130 Starnberg, FRG*2 Gynecologic Clinic, Clinic Center Großhadern, Ludwig-Maximilians-University Munich, W-8000 Munich 70, FRG

Abstract: A total of 56 patients were recruited to a randomized double blind study (28 to the enzymes and placebo group, respectively) and treated for a period of 28 days in order to evaluate the effectiveness and tolerance of an enzyme combination preparation as adjuvant of the initial 6-day basic antibiotic treatment.
At the beginning of the investigation there were no differences between the enzymes and the placebo group regarding the parameters characterizing the process of recovery. At the end, however, such differences were observed: body temperature in the enzymes group 37.0°C, in the placebo group 37.2°C, p = 0.021; WBC in the enzymes group 8,800/m l, in the placebo group 10,100/m l, p = 9.52 x 10-6; ESR after 1 h 14.8 mm/h and 19.5 mm/h in the enzymes and placebo group, respectively, p = 0.003; score for palpable tumors in the enzymes group 1.0 ("more resistant to touch than normal

on one side") and 3.0 in the placebo group ("bilateral resistance to touch"), p = 1.28 x 10-7; score for tenderness on pressure in the enzymes group 0 (nothing abnormal detected) and 2 in the placebo group (uterus and adnexa), p = 4.42 x 10-7; score for vaginal discharge in the enzymes group 0 ("white/normal") and 1 in the placebo group ("slightly purulent and/or sanguineous"), p = 1.39 x 10-6.
The adnexitis score, defined as major criterion of effectiveness, gave corresponding results: with comparable baseline values (enzymes = 12.2, placebo = 11.3, p = 0.08) it was 2.6 in the enzymes group (subacute adnexitis) and 7.7 in the placebo group (moderate adnexitis) at the end of therapy (p = 7.45 x 10-7).
The results of this study suggest that the enzyme combination preparation used is effective as adjuvant of basic antibiotic treatment in acute adnexitis. There were no side effects in either group.
Key words: Therapy of adnexitis - adjuvant enzyme therapy - enzyme combination preparation vs. placebo - antiinflammatory effect

Systemic enzyme therapy in the treatment of chronic salpingitis and infertility.

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. Institute of Pediatrics, Obstetrics, and Gynecology, Ukraine. [Ukrainian, Czech]

30 women, mean age 26.5 years, with chronic salpingitis and infertility were observed. 18 women suffered from primary infertility, 12 from secondary one. 21 patients were previously treated (antiinflammatory, hormonal therapy). 27 patients were diagnosed with unilateral salpingitis, 3 with bilateral one. Treatment started after activation of chronic inflammatory process. First, pyrogenal was administered, followed by antibacterial, anticandidous, desensibilization, and vitamin therapy. Together with antibiotics, Wobenzym® was administered at the dose of 5 dragees 3 times a day for 10 days. Patients in the control group received the same therapy without Wobenzym®.
Already after 5-6 days of Wobenzym® treatment, an improvement of patients condition was observed. Frequency and intensity of abdominal pain and in 86.4 % normalization of body temperature, appetite and intestinal function was seen. Positive changes of inflammatory signs were found after treatment - decreased infiltration, disappearance of pain on palpation. Positive status was verified also by blood parameters: leukocyte count decreased from 8.0 ± 0.3 x 109 to 6.3 ± 0.1 x 109. Sedimentation normalized and concentration of C-reactive protein decreased under Wobenzym® treatment. Above described parameters did not change in the control group.
In 20 out of 22 patients, normalization of microflora was found. Impaired menstrual cycle normalized in 75 % patients.

Wobenzym® in complex therapy of actinomycosis of abdominal cavity and small pelvis in women.

Mirzabalaeva A.K., Klimko N.N., Yarobkova N.D. Wobenzym® in complex therapy of actinomycosis of abdominal cavity and small pelvis in women. Problemy medicinskoj mykologii 1999, Vol. 1., No. 1, pp. 45-50. [Russian, Czech] Kashkin Research Institute of Medical Mycology, Saint Petersburg Medical Academy of Post Graduate Education, Russia

36 patients in the age from 18 to 49 years (average age in years – 38.8) were treated. Clinical variants of actinomycosis have been manifested by endometritis, salpingitis, salpingoophoritis or liver abscesses. The diagnosis was established basing on hystological research of endometrium smears and bioptat with the detection of specific actinomycotic granuloma. The therapy with the wide spectrum antibiotics was carried out to all the patients; 14 patients received Wobenzym® during 6 weeks – 5 dragees 3 times per day with antibacterial therapy. The control group included 22 patients. Patients in comparison groups did not differ by age, duration and localization of disease.
Average duration of treatment of patients with Wobenzym® was of 4.5 months and 8.5 months in control group. In patients receiving Wobenzym® the repeated surgical operations were not carried out, in control group the frequency of repeated operations was of 31.8 %.

PROSTATITIS & COPULATORY DYSFUNCTION

In men, Wobenzym® is a very efficient therapy for both bacterial and abacterial prostatitis, and also relieves the sexual dysfunction that typically accompanies prostate diseases.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:

Using Wobenzym® for Treating Diseases of Brain & Nervous System
Hormones & Wobenzym®

What the literature says about Wobenzym® and PROSTATITIS & COPULATORY DYSFUNCTION DUE TO PROSTATITIS

PROSTATITIS & COPULATORY DYSFUNCTION DUE TO PROSTATITIS

Phlogenzym® in the Treatment of Chronic Prostatitis

Schlüter, P. Phlogenzym® in the Treatment of Chronic Prostatitis. PharmaScript, Primelweg 2, D-82538 Geretsried, Germany. Date of report: October 30th, 1997 Study No.: MU-694422 Randomised double-blind study phase III with parallel groups vs. placebo according to the guidelines of good clinical practice (GCP) Integrated final report according to ICH E3 guidelines Primary Investigators: Peter Schlüter, M.D. Gartenstrasse 16, D-69502 Hemsbach, Germany Evaluation by: MUCOS Pharma GmbH & Co Clinical Research Dpt. Malvenweg 2, D-82538 Geretsried, Germany Report by: PharmaScript, Primelweg 2, D-82538 Geretsried, Germany

Summary: In this double-blind clinical study efficacy and tolerance of Phlogenzym® was tested in patients with chronic prostatitis. It was compared with placebo.80 patients were planned, 40 patients received the enzyme preparation Phlogenzym® (enzyme group), and 40 patients placebo (placebo group). The recruited patients were subdivided into strata with bacterial prostatitis and abacterial prostatitis. In the enzyme group 17 patients had a bacterial and 23 an abacterial prostatitis and in the placebo group 19 patients were treated because of a bacterial and 21 because of an abacterial prostatitis. The data of all patients was evaluable.

The trial was carried out by Peter Schlüter, M.D., Gartenstrasse 16, D69502 Hemsbach, Germany.

Each patient received 2 tablets t.i.d. (i.e. 6 tablets per day) of the "enzyme tablets". In one group (enzyme group) the patients received Phlogenzym® and in the other group (placebo group) placebo tablets.

At baseline the patients were comparable with regard to age, height, weight (except the patients with abacterial prostatitis), manifestation of current prostatitis, last relapse, manifestation of the 1st prostatitis, and frequency of relapses in the previous year (except the patients with bacterial prostatitis): $p > 0.05$, Wilcoxon-Mann-Whitney-U-test.

As main endpoint for statistical evaluation a sum score calculated from perineal pain, lumbar pain, inguinal pain, testicular pain, defecation pain, fever, miction, strangury, dysuria, nycturia and burning when urinating after two weeks of therapy was defined.

As secondary criteria the various kinds of pain and symptoms, the consistency of the prostate, the state of the urine, the adverse events, and the global judgements by the physician and by the patients were evaluated descriptively. The main endpoint showed statistically significant differences ($p > 0.05$) in the evaluation of all patients and of the strata with both bacterial prostatitis and abacterial prostatitis. The Mann-Whitney statistics allow the conclusion of superiority of the enzyme preparation, in all patients and in patients with abacterial prostatitis there was a big relevant difference (Mann-Whitney statistics: > 0.71), and in patients with bacterial prostatitis there was a medium relevant difference (Mann-Whitney statistics: > 0.64).

The secondary endpoints perineal pain, testicular pain, miction, strangury, and nycturia were significantly better in the enzyme group in all patients, and in both strata. Inguinal pain and dysuria were significantly better in the enzyme group in all patients and in abacterial prostatitis. Defecation pain was better in the enzyme group in all patients and in bacterial prostatitis. Inguinal pain was significantly better in the placebo group in bacterial prostatitis.

The urinalysis (tested by test strips: leukocytes, erythrocytes, protein, and sediment) improved in all patients.

In the tested laboratory parameters (creatinine, urea, Quick-value, gGT, AST, ALT, a1-antitrypsin, a2-macroglobulin, C-reactive protein, ceruloplasmin, a1-glycoprotein, haptoglobin, fibrinogen, total protein, albumin, a1-globulin, a2-globulin, b-globulin, g-globulin, IgG, IgA, IgM) only seven values deteriorated within a limit of ± 15%, all other values remained unchanged or improved.

The efficacy of the drug was judged in the enzyme group by the physician and by the patients as "very good" to "good". In the placebo group the physician and the patients judged the efficacy of the drug as "moderate" to "unsatisfactory". There were statistically significant differences between the groups ($p < 0.0001$). The tolerance of the drugs was judged by the physician and by the patients in the enzyme group as "very good" to "good" and in the placebo group as "good".

There were statistically significant differences between the groups ($p < 0.05$).

Adverse events were documented in 25 patients in the enzyme group (mainly gastro-intestinal complaints or inflammations), and in 15 patients in the placebo group (mainly inflammations), most of them not related to the test drug. They started on average after 16.8 days in the enzyme group and after 18.3 days in the placebo group. The duration was 6.4 days in the enzyme group and 7.5 days in the placebo group. They were judged as "moderate" in both groups. The patient's outcome was without damage. The difference between the groups was statistically significant in favor of the placebo group ($p < 0.05$).

Efficacy and tolerance of oral enzyme therapy in chronic prostatitis: Results of a double-blind therapy study.

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. PZ 15 (5-07-3) [Czech]

An orally applied enzyme preparation Phlogenzym® of bromelin, trypsin and the flavonoid rutosid was tested for efficacy and tolerance in chronic prostatitis. The therapy test was conducted as a randomized double-blind clinical trial in a group of 80 voluntary men aged between 18 and 72 years who were recruited from the investigating general practitioner's clientele of patients after they had declared their informed consent. The group was divided up into two of 40 test persons each: an ''enzyme group" and a "placebo group". The two groups were subdivided into strata with bacterial prostatitis and abacterial prostatitis. For the test-therapy period of four weeks each patient received 180 "enzyme tablets", either active tablets or placebo in all, to take 2 tablets t.i.d. (6 tablets per day). The patient's compliance to the test therapy was established by count of the tablets he returned after four weeks.

Through six examinations altogether - the first at the beginning of a patient's test period, then four follow-ups every week after baseline and a final one four further weeks later - the course of pain and symptoms characteristic of prostatitis was documented. At the same occasions urinalyses and palpations of the prostate's consistence were done additionally, whereas adverse events were recorded and treated only at the four follow-up recalls in between baseline and final examination.

A sum score calculated from the degrees of severity of the various kinds of pain and symptoms after two weeks of therapy was defined as the main endpoint for statistical evaluation. As secondary criteria the courses of pain and symptoms, also of the prostate's consistency and of the urinalyses during the four-week test therapy were evaluated descriptively, together with the global judgements of the therapy's efficacy and tolerance by the physician and the patient. The laboratory parameters of the patients at beginning and end of the therapy as well as the patients outcome from adverse events which occurred during that period, were documented and evaluated as safety variables.

A level of 5 % for the significance of differences was defined as model of the statistical test. The comparability of the groups at baseline and the differences between them in the reactions to the test therapy were statistically evaluated by the Wilcoxon-Mann-Whitney U-test.

The main endpoint as well as the secondary-criteria endpoints showed statistically significant differences ($p < 0.05$) between the test groups and the strata within them. The Mann-Whitney estimators allow the conclusion of a superiority of the enzyme preparation; the relevant difference was big in all patients and in the patients with abacterial prostatitis, medium in patients with bacterial prostatitis. Urinalyses improved in all patients, laboratory parameters remained unchanged mostly and improved in some cases.

As judged by the physician and the patients, the efficacy of the therapy was "very good" to "good" in the enzyme group and "moderate" to "unsatisfactory" in the placebo group. The tolerance was judged as "very good" to "good" in the enzyme group and "good" in the placebo group. Adverse events were documented in 25 patients of the enzyme group (mainly gastrointestinal complaints or inflammations) and in 15 patients of the placebo group (mainly inflammations), mostly judged as "moderate" and in all cases treated symptomatically. The patients outcome was without damage.

Special treatment of patients suffering from a mixed copulatory dysfunction with interoreceptive syndrome.

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. [Russian, Czech]

A total of 38 patients suffering from a mixed copulatory dysfunction were recruited into the trial. Twelve of them were at the age ranging from 20 up to 30 years, fourteen at the age from 31 to 40 years, eight at the age from 41 to 50 years and four at the age from 51 to 60 years. Microbiological investigation of a prostate secreta revealed following microbial agents: E. coli in 14 patients (36,8%), Trich. vaginalis in 10 patients (26,3%), Staph. aureus in 5 patients (13,2%), Str.faecalis in 4 patients (10,6%), Proteus in 3 patients (7,8%) and Klebsiella in 2 patients (5,3%). An impaired copulatory function was observed. Libido was reduced in 8 patients, erection was impaired in 38 patients (100%), ejaculation was

impaired in 12 patients (31.6%). At the first stage of the treatment, antibiotics were administered according to the results of the investigation of a microbial agents susceptibility.
In order to minimize the ts of antibiotic side effects, a combination enzyme preparation Wobenzym® was included into the treatment. Its antiflogistic and immunomodulatory effects have been reported (Repina A.M., 1997). The patients were divided into two groups, each consisting of 19. The first group was treated with antibiotic (and in some cases antiprotozoic) drugs in combination with Wobenzym® in doses 3 - 5 tablets three times a day 30 - 40 minutes before meals for 2 - 3 weeks. The second one group was treated without Wobenzym®. The treatment was more succesful in the enzyme group (89.5% of recovery) in comparison to the control one (68.4% of recovery). The second stage of the treatment was concerned in a removal of psychogenic syndrome by means of psychotherapy and psychotropic drugs.
In summary the libido increased in all 38 (100%) patients, erection was improved in 32 (84.2%) patients and a positive therapeutic effect was achieved in 29 (75%) patients suffering from the impaired erection.

Systemic and local enzyme therapy used in combination with transurethral drainage of prostate in patients with obstructive forms of chronic prostatitis.

Guskov A.R., Bogatcheva I.D., Iatsevitch G.B. Systemic and local enzyme therapy used in combination with transurethral drainage of prostate in patients with obstructive forms of chronic prostatitis. Urologia i nefrologia 1998, No. 6, pp. 37- 42. [Russian and Czech] Research and Treatment Center of Non-Operative Urology and Andrology, Moscow

In our study, we focused on the complex treatment by a transurethral drainage and use of proteolytic enzymes, thus aiming to lyse the "plugs" and to diminish the viscosity of inflammatory products. This could, by our opinion, significantly accelerate restoration process of the affected organ. Aim of the presented work - to study the effect of combined systemic (Wobenzym) and local (in situ electrophoresis of trypsin and chymotrypsin) enzyme therapy on the efficacy of transurethral prostate drainage (electrostimulator-aspirator "Intraton-4") in patients with chronic prostatitis and to investigate its mechanism.
530 patients with chronic prostatitis were observed. Examinations and treatment were done at the out-patient clinic. All patients underwent, besides general clinical examinations, analysis of urine in two portions, test on pathogenic microflora, gonococcus, trichomonad, chlamydia, mycoplasma, ureaplasma using direct and indirect fluorescence, and also diagnostics of urethral infections using PCR. Patients with clinical signs of acute urethritis received anti-inflammatory therapy with regard to the manifested pathogenic microflora. All patients were subject to the ultrasound (US) examination of prostate using polypositional rectal apparatus "Pie Medical" (transurethral ultrasound examination) (8). Patients were US monitored during treatment. Patients with the presence of microabscesses and "pseudomicroabscesses" in the prostate were subject to the complex therapy including transurethral vacuum drainage of prostate ("Intraton-4") combined with in situ electrophoresis (urethral, rectal, or urethro-rectal) of trypsin and chymotrypsin and Wobenzym® administration - 5 dragees 3 times a day.
A positive restoration dynamic in patients without Wobenzym® reached 100% after 30 days of treatment, while in Wobenzym-treated patients the same result was obtained after 20 days.
A complete prostate drainage (disappearance of microcavities of irregular and drop-like form on US) after 20 days of treatment without systemic enzyme therapy was achieved in 52% of patients, while in Wobenzym-treated patients - in 88.2%. We show a case report of US data - patient X., aged 28 years.
The most important are comparison results of prostate drainage intensity in both groups of patients over the first 10 days of treatment. In the group without systemic enzyme therapy, a complete drainage of prostate was achieved in just 5% of patients, while in the Wobenzym-treated group - in 47.2 % of patients, i.e. nearly 10 fold.

PSORIASIS

Psoriasis is another one of those conditions that require dietary changes as well. But even then, it is difficult to get rid of because – again - because the body is stuck in a chronic cycle of inflammation.
Psoriasis is another one of those conditions that have high amount of the pro-inflammatory cytokine TNF-alpha (tumor necrosis factor alpha). It is known that TNF alpha is elevated in both the skin patients with psoriasis. We also know that Wobenzym® decreases TNF-alpha levels.
So, it should come as no surprise, when we learn that when Wobenzym® is used, there is a marked improvement of clinical symptoms and as well as laboratory values in patients with psoriasis.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Skin Conditions & Wobenzym®

What the literature says about Wobenzym® and PSORIASIS

Wobenzym® in the treatment of patients with psoriasis.

Milus I.E. Wobenzym® in the treatment of patients with psoriasis. Zurnal dermatologii i venerologii 1998, 2 (6), 35-36. [Ukrainian] vDonetsk Medical University.

58 patients (37 women, 21 men), aged 2-58 years, suffering from various forms of psoriasis were observed. All patients underwent complex, clinico-laboratory examination.
Patients were divided into 4 groups: Control - 15 patients, received a conventional therapy (vitamins, biostimulators, immunocorrectors, fyziotherapy, and softening ointments).

- Complex treatment including Wobenzym® (3 tablets 3 times a day for 30 days) - 16 patients
- Complex therapy including external application of Wobe Mugos ointment - 6 patients
- Complex therapy including both Wobenzym® and Wobe Mugos - 21 patients

Treatment was well tolerated by all patients. In patients in groups 2 and 4, receiving Wobenzym®, a significant decrease of exsudative component of exacerbation was observed after 3-5 days of treatment. Resting stage of the disease occurred in group 1 after 7-9 days of treatment, in patients in groups 2 and 4 after 3-5 days. Complete regression was achieved in group 1 after 28-32 days of treatment, in group 2 after 24-26 days, in group 3 after 26-28 days, and in group 4 after 18-20 days. Dynamics as well as the exacerbation regression were accompanied by a marked tendency to the normalization of biochemical, immunological parameters (most significant in groups 2 and 4).
Results obtained within one year proved a high efficacy of polyenzyme preparations in the complex treatment of psoriasis. Disease recurrence within 6-12 months was diagnosed in 6 out of 15 patients in group 1, while only in 7 out of 37 patients in enzyme treated groups 2 and 4.

Systemic enzyme therapy in dermatology and venerology: perspectives of its use.

Protsenko T.V. Systemic enzyme therapy in dermatology and venerology: perspectives of its use. Zurnal dermatologii i venerologii 1998, 2(6), c.12-13. State Medical Uiniversity, Donetsk, Ukraine [Abstract in Russian.]

255 patients (36 – chlamydiosis, 46 –lues, 43 – psoriasis, 48 – sclerodermia, 35 – various forms of alopecia, 25 – granuloma anulare, 22 – lipoid necrobiosis) were observed for more than 2 years.
Especially important was a complex treatment of chlamydiosis and lues patients combined with Wobenzym®. Patients received Wobenzym® 5-3 dragees 3 times a day in combination with conventional antibacterial therapy. SET enhanced significantly therapy efficacy, in some cases even enabled to omit conventional drugs.
Patients suffering from dermatological diseases received Wobenzym® (9-15 dragees daily for at least 4 weeks) and Wobe-Mugos ointment locally. A marked improvement of clinical symptoms and laboratory parameters was seen in 61.5% patients, improvement in 19.8%.
No side-effects were reported in all 255 patients.

PYELONEPHRITIS

In a study of 66 patients with chronic pyelonephritis, Wobenzym® yielded results that "considerably exceeded those in conventional drug treatment." This was evidenced by both clinical findings (symptoms) as well as laboratory findings. One reason for the notable benefit would be due to the normalization of urinary system local immunity, as we just discussed.

Now I will be the first to admit that kidney infections are serious conditions, and antibiotic therapy is very appropriate therapy. But what we have observed is that chronic and recurrent infections – infections that are resistant to improvement even on antibiotics – do much better – and can be resolved when Wobenzym® is added to the treatment plan. Other conditions that are often resistance to antibiotic therapy and benefit from this systemic enzyme therapy also include and recurrent urinary tract infections, a very common problem of the urinary system.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Kidney and Bladder Conditions & Wobenzym®

What the literature says about Wobenzym® and PYLONEPHRITIS

Clinico-laboratory evaluation of treatment efficacy in chronic pyelonephritis patients with Wobenzym®.

Schved N.I., Martyniuk L.P. Clinico-laboratory evaluation of treatment efficacy in chronic pyelonephritis patients with Wobenzym®. Vratschebnaya praktika 1997, 4, 38-42. Ternopol medical academy. [Abstract available in Russian.]

Abstract: The influence of Wobenzym® on pathogenetic mechanisms of chronic pyelonephritis and its therapeutic effect was observed. The results of treating 66 patients with chronic pyelonephritis were presented. The investigation revealed that Wobenzym® enabled to receive positive clinico-laboratory results, which considerably exceeded those in conventional drug treatment. Therapy with Wobenzym® resulted improving immunology and rheology blood induce normalising parameters of lipid peroxidation and antioxidant system as well. Key words: chronic pyelonephritis, Wobenzym®, immunology, rheology, lipid peroxidation, antioxidant system.

Coenzyme metabolic assurance of patients with recurrent nephrolithiasis in the complex treatment by systemic enzyme therapy.

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. Odessa Medical University, Department of Urology, Odessa, Ukraine. [Abstract available in Ukrainian.]

In addition to clinico-immunological investigation, the metabolic supply of enzymatic systems with pyridoxal phosphate and thiamin pyrophosphate was studied in 50 patients with recurrent nephrolithiasis complicated by chronic pyelonephritis. It was established that the value of thiamin pyrophosphate - effect was reliably increased in patients with nephrolithiasis, this witnessing the insufficient metabolic supply with coenzyme form of vitamin B1-cocarboxylase. There was a strong tendency to the growth of pyridoxal phosphate-effect. The complex treatment of patients included antiinflammatory, antibacterial therapy, as well as operative intervention in the upper urinary tract. 25 patients additionally received polyenzyme preparation Phlogenzym in the early postoperative period (for 2-3 weeks) and as out-patients (for 2 weeks more).

The complex treatment of nephrolithic patients with the use of Phlogenzym produced marked normalizing influence on the value of pyridoxal phosphate-effect which is indicative of the reduction of alterations in the urinary tract tissues. The postoperative period had a favourable course, and the control check-up carried out 12 months later revealed that the incidence of lithogeny recurrence was reliably lower than in the control group.

RESPIRATORY TRACT INFECTIONS

In two separate studies, we have seen that Wobenzym® dramatically reduces the sickness rate in children that have frequent infections. The sickness rate in Wobenzym-treated children was reduced by 65.2 % and reduction of antibiotic consumption was 71.8 %. The decreased need for antibiotics is of course impressive. On average, the children were sick over 5 times a year before taking Wobenzym®. Atfer taking Wobenzym® they got sick less than twice a year. The Wobenzym-treated children also benefited from not having elevated temperature and feeling less tired.
We should keep in mind, that in these cases the children were traditionally treated with antibiotics, but the course of the infection took long to resolve, and the patients had recurrent infections – they were in and out of the hospital over 5 times a year.
Wobenzym® is used as an adjuvant in these cases to make antibiotics more effective - but more importantly to improve immune function so that the patients did not keep getting sick. So Wobenzym® acted as both an adjuvant and as an immunomodulator – restoring balance to the immune system.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Respiratory Conditions & Wobenzym®

What the literature says about Wobenzym® and RESPIRATORY TRACT INFECTIONS

Systemic enzyme therapy in the treatment of children with recurrent infections of respiratory tract.
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. [Czech]
The article summarizes a four-year-experience with use of systemic enzyme therapy in the treatment of recurrent respiratory diseases in children.
Efficacy of Wobenzym® in the treatment of recurrent respiratory infections was studied in children treated during 1997-1999 in the pediatric and allergology and clinical immunology practice. 30 children, aged 3-15 years, showing a high sickness rate and deviation of at least one of the tested immune parameters (reduced IgA, IfM, IgG, CD3 or elevated IgE) were included into the study. The most frequent diagnoses were recurrent bronchitis (15 children), proven asthma bronchiale (6 children), and recurrent laryngitis (4 children) accompanied by rhinitis, pharyngitis, tonsillitis, and otitis. 9 children suffered additionally from atopic eczema.
Children received Wobenzym® at the daily dose of 1 coated tablet per 6 kg body weight. Daily dose was divided into 2-3 subdoses. Treatment started in autumn and lasted for 6 months. Prior to the start of Wobenzym® treatment children underwent basic laboratory examinations, smears from nose and throat, ORL examination, and screening for basic parameters of cellular and humoral immunity.
Wobenzym® treatment led to a reduction of recurrence and dyspnea attacks in patients suffering from recurrent bronchitis. Moreover, frequency of acute respiratory infections as well as number and severity of dyspnea attacks decreased also in children with proven asthma. In case of recurrent laryngitis patients there were basically no more laryngeal dyspnea attacks observed, whereas prior to the Wobenzym® treatment nearly every banal respiratory infection resulted into such attack. Even if the disease occurred, its severity was mild and administration of corticoids, so far necessary at each laryngitis attack, was not necessary anymore. In children with atopic eczema, a marked improvement of skin condition was observed and outlasted for several months after end of Wobenzym® therapy.
Before treatment, elevated levels of IgE were found in 50 % patients. Wobenzym® therapy resulted in reduction of primarily elevated IgE levels in 93 % patients. IgA level before treatment was elevated in 33 % of patients. Wobenzym® treatment led to an IgA normalization in 60 % patients. In 30 % patients IgA level increased, although it did not reach the normal values, yet.
Furthermore, clinical documentation of another 109 patients treated with Wobenzym® in 1999-2001 was evaluated aiming to study the efficacy of Wobenzym® in the treatment of recurrent respiratory diseases. Study group consisted of children up to 10 years – 74 % (42 % children up to 6 years, 32 % children 6-10 years), 13 % children and youth 10-18 years, 13 % patients older than 18 years. The most frequent immunological deviations were elevation of IgE levels (41 % patients) and decreased IgA levels (20% patients).
Patients used mainly Wobenzym®, in some cases Phlogenzym. Treatment duration was 6 months. Children used Wobenzym® at the recommended dosage, usual daily dose for adults was 3x 4-5 coated tablets. Daily dose of Phlogenzym for adults was 3x2 tablets. In children, Phlogenzym was preferred in the treatment of laryngitis.
Daily dose of Phlogenzym for children was 1 tablet per 10 kg body weight.

Systemic enzyme therapy resulted in reduction of both frequency and severity of diseases. Therefore, associated prescription of antibiotics was also significantly reduced. Regarding the laboratory results, reduction or normalization of IgE values was found in 47 % enzyme-treated patients; lowered IgA levels were adjusted in 64 % patients. Very interesting were the results concerning ECP (eosinophil cationic protein) – a marker of atopic inflammation.
Elevated ECP levels were measured in 20 patients (20 %) before start of enzyme treatment. After the treatment, decrease of elevated ECP levels was found in 18 out of 20 patients.
Summary of findings for individual diagnoses:
Recurrent tonsillitis – children repeatedly suffering from tonsillitis and using antibiotics were first treated with combination of antibiotics and Wobenzym®. If the laboratory examination performed at disease recurrence did not prove a streptococcal tonsillitis, only Wobenzym® and antipyretics were administered. Tonsillitis course was gradually palliated, frequency of disease attacks decreased and in number of patients disappeared completely.
Recurrent laryngitis – systemic enzyme therapy suppressed laryngeal dyspnea and through its immunoregulatory effect caused lowering of sickness rate. Phlogenzym was often preferred in combination with basal treatment.
Atopic eczema – positive effect of Wobenzym® was reached by a systemic effect on inflammatory process. However, an improvement of skin condition was observed after long term (3 months) treatment accompanied by further dietetic and regimen measures. Improvement outlasted after discontinuation of therapy. Asthma bronchiale – systemic enzyme therapy was a suitable supplementary treatment, it reduced frequency of acute diseases and often enabled to reduce a dosage of inhalation corticoids.
It can be concluded that systemic enzyme therapy represents a novel therapeutic modality helping in the treatment of children showing a high sickness rate.

Therapeutic efficacy of Wobenzym® in patients with focal pneumonia.

Shved M.I., Dubkova G.I. Therapeutic efficacy of Wobenzym® in patients with focal pneumonia. Visnik naukovych doslidženij 1999, No. 2, pp. 79-82. [Russian abstract, Czech abstract]

The article provides the investigation of two treating methods (the commonly-spread one and the other – combined with the Wobenzym) influence upon the clinically-roentgen indications, immune activity, and the condition of the lipid freeradicaloxidation in 51 patients with the nidus pneumonia. There were determined such changes in patient's state: the decrease of the T-h and T-c lymphocytes, the humoral immune part activation, and the balance disturbances in the antioxydative protective systems functioning. The complex therapy with the Wobenzym® gives a possibility to reach more effective clinically-roentgen and laboratory sanation in short time period due to normalization of the immune reactivity and processes of the lipid freeradicaloxidation.
Key words: nidus pneumonia, Wobenzym®, lipid peroxidation, antioxydative protective system, immune reactivity (status).

Systemic enzyme therapy as a helpful aid in the pediatric practice.

Hubková B. Systemic enzyme therapy as a helpful aid in the pediatric practice. VOX PEDIATRIAE 2003: Roè. 3, è. 3, pp. 30 – 31. [Czech abstract]

Based on first positive experience with Wobenzym® treatment in 4-years old boy suffering from recurrent infections, systemic enzyme therapy was successfully used also in other children showing a high sickness rate, which were repeatedly treated with antibiotics.
37 children, aged 1,5 – 18 years, included into the study used Wobenzym® during 1999-2001 and were evaluated during 12 months prior and after start of Wobenzym® treatment.
Sickness list in the evaluated group of children:
13 children with proven allergies, recurrent infections of respiratory tract, including bronchitis (5 children with dermorespiratory syndrome),
6 children with recurrent bronchitis without proven allergy,
5 children after severe pneumonias (3x atypical pneumonia),
4 children with recurrent tonsillitis,
4 children with recurrent renal and urinary tract diseases (2 children with pyelonephritis and 2 children with cystitis),
2 children with recurrent laryngitis,
1 child with recurrent otitis,
2 children with recurrent viral infections showing a severe course.
Children were treated with Wobenzym® at the daily dose of 1 coated tablet per 6 kg body weight. The dosage was divided into 2 daily doses and administered on empty stomach. Small children who were unable to swallow the whole tablet used

crushed tablets strictly on empty stomach with plenty of water. Daily dosage was divided into 2 doses. Daily dose in these cases was increased to 1 coated tablet per 4 kg body weight.
Prior to the start of systemic enzyme therapy, children underwent basic laboratory examination, blood count, immunoglobulins, and other necessary examinations associated with the individual diseases. Children were in most cases treated for 6 months from autumn to spring. During Wobenzym® treatment as well as six months prior and after the treatment children received no immunostimulatory drugs.
For study evaluation, a mean sickness rate in Wobenzym-treated children was observed within 12 months prior the treatment and next 12 months after the start of treatment. This period consisted of 6 months of Wobenzym® treatment followed by 6 months of no treatment. For comparison purposes, a mean annual sickness rate in all children in the practice during last 3 years was calculated. All diseases, including diarrheal ones accompanied by fever higher than 37.2 °C, infectious diseases with or without fever (e.g. varicella), attacks of allergic cough, pollinoses without fever where a current medication was insufficient, were included into the evaluation. Injuries were excluded.
A total annual sickness rate in 1999 was 3.8, in 2000 - 4.2, and in 2001 - 3.2.
Thus, a mean annual sickness rate calculated for the above three years was 3.7.
One year before start of Wobenzym® treatment each out of 37 observed children got sick 5.4 times a year. During the year of Wobenzym® treatment the same patients got sick only 1.8 times a year. Even more interesting were the results showing consumption of antibiotics necessary to treat the disease. One year before Wobenzym® treatment, the children used antibiotics in total of 71 cases, whereas 1 year after start of Wobenzym® treatment it was just 20 cases. Therefore, a sickness rate in Wobenzym-treated children was reduced by 65.2 % and reduction of antibiotic consumption was 71.8 %.
Very interesting results were obtained in small children using crushed tablets.
This in principle non lege artis mode of administration of tablets resistant to gastric juices was chosen after thorough consideration in patients suffering from recurrent laryngitis which did not respond to any other treatment options. Therapeutic effect was seen also in such administered crushed Wobenzym® tablets, laryngitis does not recur anymore. Although in one patient first laryngitis recurrence occurred 13 months after the start of Wobenzym® treatment, disease course was mild and easily treatable.
Significant improvement in skin condition was observed in five patients with dermorespiratory syndrome. However, it should be mentioned that the improvement was seen after long-term Wobenzym® treatment – at least 8 weeks.
Reduction of allergic manifestations, such as nose obstruction and burning eyes during pollen season which persisted even under treatment with antihistamines, was observed in children with proven pollinoses under Wobenzym® treatment. Children used concomitantly Wobenzym® and current antihistamine preparations. In comparison to the treatment with other immunostimulatory drugs, Wobenzym-treated children benefited from not having elevated temperature and being tired.
Based on the above mentioned findings it can be concluded that systemic enzyme therapy may serve as a very helpful aid in the treatment of children showing a high sickness rate. Sickness rate is reduced as well as a necessity to use antibiotics. In chronically sick children Wobenzym® represents a suitable supplementary treatment.

RHEUMATOID ARTHRITIS

As you may know, **rheumatoid arthritis** (often called RA) is a chronic systemic inflammatory disorder that primarily attacks the joints – although other tissues may be inflamed as well. Rheumatoid arthritis is an autoimmune disease, so it is often treated with high dosages of steroid hormones or other powerful drugs like methotrexate, or gold salts, or high dosage NSAIDs.

Because rheumatoid arthritis is an autoimmune disease there are increased amounts antibodies, such as Rheumatoid Factor and IgG-RF. This can result in increased **circulating immune complexes,** which, as we mentioned earlier, are quite pro-inflammatory. We also see increased levels of proinflammatory cytokines such as **TFN-alpha** (tissue necrosis factor – which, as the name implies, promotes destruction of tissue). As you would expect, there are also increased levels of **C-reactive protein**. In contrast to osteoarthritis – which is a degenerative process, rheumatoid arthritis is an actively destructive process.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Joint Pain & Wobenzym®

What the literature says about Wobenzym® and RHEUMATOID ARTHRITIS

Wobenzym® in therapy of rheumatoid arthritis

Guseinov N.I. Wobenzym® in therapy of rheumatoid arthritis. International Journal on Immunorehabilitation 2001, Vol. 3, No. 2, pp. 73-74. Proceedings of the VII International Congress on Immunorehabilitation "Allergy, Immunology and Global Network: Insight into the New Millennium" New York, USA, April 14 – 17, 2001

By now there are no precise indication to select basic preparations while treating rheumatoid arthritis (RA). The basic treatment of RA is limited by the risk of adverse drug reactions. There are no non-toxic basic preparations for this purpose except of polyenzyme preparations.

74 patients with RA underwent ínvestigation. Group I (n=40) received Wobenzym® 30 tablets daily during the first month, then 15 tablets daily for a long-term treatment. Group II (n=34) received Tauredon as basic therapy in a standard way: 1 week, 10 mg/day; 2 weeks, 20 mg/day, 3 weeks, 50 mg/day, 4 weeks till the 20 week 50 mg/day. In both groups, non-steroid anti-inflammatory drugs were administered additionally as basic therapy (150-200 mg/day). Both groups were comparatively equal in clinical-laboratory characteristics. The influence of basic therapy on the evolution of joint syndrome was studied in the dynamics of clinical and laboratory indicators. Our results showed that the defínite signs of RA remission appear at the end of the first month in t group 1 and in the group II at the 3-4 months. The dose of non-steroid anti-inflammatory drugs was reduced, respectively. This confirms the literature data on the basic properties of Wobenzym® therapy.

The results of long-term use of Wobenzym® in complex management of rheumatoid arthritis.

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. [Czech]

Open controlled one-year study of 60 patients with confirmed diagnosis of rheumatoid arthritis was conducted. Of those 30 received 7 tablets of Wobenzym® (Mucos Pharma, Germany) three times a day (group 1), another 30 patients received a weekly dose of 7.5 mg of Methotrexate (group2) (control). The both groups were matched by sex, age, clinical and laboratory data. The majority of the patients in both groups also received Diclofenac (100-150 mg/day), while some patients received the daily dose of 7.5-10 mg Prednisolone. The universally accepted clinical and laboratory indices were assessed before the treatment 3, 6, 9 months after the beginning and on completion of the therapy.

The onset of therapeutic effect (diminishing of the pain intensity, morning rigidity, Ritchi's index, inflammatory and immune activity etc.) in cases of complex management with Wobenzym® was observed as early as 1-2 months after the beginning of the therapy, while in the control group the same effect was observed only after 3-4 months. In the course of the study the medicine was withdrawn in 8 patients (26.6%) of the group 1 and in 7 patients (23.3%) of the control group because of its inefficiency. Besides, in 4 patients of the control group Methotrexate was withdrawn due to side effects. In the majority of patients of the both groups who endured the one-year course of therapy no X-ray and ultrasonographically confirmed progress of the above pathology was observed.

The Efficacy of Systemic Enzyme Therapy in the Treatment of Rheumatoid Arthritis.

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.

Summary: A total of 156 patients with rheumatoid arthritis were enrolled in a clinical study on safety and efficacy of oral enzyme therapy in a treatment involving methotrexate and NSAID. One group (n=65) received methotrexate at a dose of 7.5-10 mg/week and NSAID, while the second group (n=91) additionally received an oral enzyme combination preparation (Wobenzym®) in a daily dosage of 15-30 dragées. The group taking enzymes showed superior efficacy in the therapy with regard to Ritchie Index (improvement: 10.7 points in group one versus 14.4 points in group two), morning stiffness (improvement: 49.6 minutes in group one versus 92.0 minutes in group two), and Lee Index (improvement: 4.2 points in group one versus 5.7 in group two). Laboratory findings showed a decrease in circulating immune complexes by 30.3 % in group one and 42.2% in group two at the end of therapy. These beneficial effects of combining oral enzyme therapy with standard therapy in rheumatoid arthritis are supported by several findings in the immunological laboratory. The serum concentrations of interferons were reduced after 6 months of therapy in the enzyme group to almost normal values as compared to two to three times higher values in the control group. The stimulated interferon production was about 70% (IFN-a), and 90% (IFN-g) increased after treatment in the enzyme group (about 20% and 30% respectively in the control group).

In addition, serum levels of proinflammatory cytokines (IL-1b and TNF-a) were significantly more reduced in the enzyme group than in the control group (control versus enzyme group IL-1b: -4.1 pg/ml versus -10.3 pg/ml; TNF-a: -75.1 pg/ml versus -179.5 pg/ml).

Pain Reduction in Rheumatic Diseases by Oral Therapy with Enzymes.

Klein G., Kullich W. Pain Reduction in Rheumatic Diseases by Oral Therapy with Enzymes. Wien. Med. Wschr. 1999, 149, pp. 577-580.

Summary: Proteolytic enzymes have analgesic effects, besides the well known antiinflammatory and edema-reducing properties. These analgesic effects are based on the inhibition of inflammation and in addition to that on direct influences on the nociceptors. All that explains the therapeutical effects of such enzymes in degenerative-rheumatic and soft tissue rheumatic diseases in which inflammatory or immunologic processes are not in the forefront. In recent years a significant reduction of pain in various rheumatic diseases, concerning these aspects, was shown in several clinical studies. The clinical trial in patients with periarthritis of shoulder showed statistical equivalence of pain reduction, whether they were treated with Phlogenzym or diclofenac. Likewise, in the trial of patients suffering from painful osteoarthritis of the knee, there was a statistical equivalence of the pain-scores, comparing diclofenac and enzymes. The study of painful vertebral-syndromes again resulted in equivalence of the treatment with NSAIDs compared to therapy with enzymes.

Our experience with Wobenzym® in the treatment of patients with rheumatoid and psoriatic arthritis.

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.

Summary: The objective of the uncontrolled trial was to assess the tolerance and safety of the preparation Wobenzym® in patients with rheumatoid and psoriatic arthritis who had other concurrent anti-inflammatory treatment and to evaluate its position in combined treatment of RA and PsA. The authors added Wobenzym®, 9 to 15 enterosolvent pills per day to anti-inflammatory antirheumatic treatment in 23 patients with RA and 4 patients with PsA because of persisting clinical and laboratory activity. Treatment lasted 16 weeks and more. The evaluation of the effectiveness of Wobenzym® by the physician was as follows: very good 33.3 %, good 54.3 % and unsatisfactory 12.4 %. The evaluation of physical capacity by the patients was as follows: 18 patients (75 %) reported a better physical capacity after Wobenzym® and only 25 % (6) had the same physical capacity. There was no case of deterioration. When evaluating clinical parameters, the authors found after four months of treatment a decline of the morning stiffness ($p < 0.01$) and a better grip strength ($p < 0.05$), reduced articular index and index of incapacity according to HAQ, which however was not statistically significant. The authors recorded a decline of FW the CRP and CIK concentration ($p < 0.01$). The concentration of alpha-2 macroglobulin, alpha-1 antitrypsin, haemoglobin and amylase values did not change significantly during treatment. The trial confirmed the favourable effect of Wobenzym® on the rheumatic process, good tolerance and safety of treatment in patients with rheumatoid diseases even in case of polytherapy.

Key words: Wobenzym® - enzyme therapy - rheumatoid arthritis - psoriatic arthritis.

Clinical and immunological criteria of activity of different rheumatic arthritis courses and their treatment by Wobenzym®.

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.

Rheumatic arthritis (RA) is a chronical disease, its pathogenesity includes deep immune system disorders with a disbalance of qualitative and quantitative composition of immunocompetent cells including functional and cell cooperation disorders (8). Joint damage is the most obvious syndrom of rheumatic arthritis. But other symptoms than joint damage mostly determine an aggressivity of the disease and its prognosis. Role and place of different components of inflammation immune complex in a rheumatic arthritis process development is beeing currently discussed. A progresive character of the disease with a formation of irreversible joint and inner organ damage, an early invalidity of patients, and a decrease of working ability define a medical and social importance of this problem as well as a necessity of continuing study of clinical-pathogenetic peculiarities of rheumatic arthritis and a search for optimal treatment program.

An important role in a rheumatic arthritis diagnosis plays a determination of IgG-RF (rheumatic factor) which seems to be an autoantibody against IgG fragment (6). Both an existence of serum negative variant of rheumatic factor and its detection in other rheumatic and nonrheumatic diseases determine a necessity to investigate RA serological markers, for example antibodies against cardiolipins (aCL), associated with thromboses during rheumatic diseases, and antibody against native DNA (n-DNA) determining a formation of immunopathological component.

In many cases a rheumatic arthritis course is complicated by systemic symptoms which cause a development of pathological process (3, 13).

Various changes in rheological properties of blood during rheumatic arthritis cause damages of microcirculation and seem to be one of the factors which make the disease become chronic (2, 20).

Despite of different clinical symptoms of thrombohemorragical syndrom and expression of damages of rheological, coagulational, and fibrinolytical properties of blood (2, 3, 7), the most important way to diagnose changes in microcirculation is the use of immunological methods.

Such methods include determination of antigen factor van Billebrand (FB) in blood plasma. FB is a macromolecular protein synthesized by the vascular endothelium cells which define a function of thrombocytes (TC) and an activity of VIII coagulating factor structural part of which FB makes (7).

Except this, investigation of new pathogenetic mechanisms of a rheumatic arthritis formation, insufficient efficacy of existing preparations for treatment, and serious side effects (treatment by corticosteroids, nonsteroidal antirheumatic substances, cytostatics) show a need for new treatment methods of different types of rheumatic arthritis.

45 patients (9 men, 36 women) with reliable rheumatic arthritis (criteria of American Rheumatological Association, 1987) were observed. An average age was 46.9 (from 23 to 76) years. 38 patients were serum positive on IgM-RF and 7 were serum negative. 5 patients showed activity of rheumatic arthritis corresponding to degree I, 24 patients to degree II and 16 patients to degree III.

Confirmation of diagnosis by X-ray for all patients is available (Table 1).

In 28 patients syndroms such as fever, rheumatic nodes, amiotrophic syndrom, damage of cardiovascular system, digestive system and others occured. In some cases, concomitant diseases appeared: tuberculosis - 1, malignant tumors - 1, diabetes - 1, periodical illness - 1.

During clinical observations of patients joint index, oedema index, joint sum (by Richi), functional test by Li and an intensity of hand clasp (mm.rt.st) were followed.

All patients were subjected to a general clinical observation and also basic signs of immunological statute (9) were observed. Using IFA a titer of antibody against n-DNA was determined. IgM-RF and a presence of antibody against cardiolipins and antigen factor von Billebrand (FB) were determined in patients serum (test of the “AGAB” system, Moscow).

Wobenzym® (Mucos Pharma) was administred together with methotrexate 15mg on Sunday; 10 dragees three times a day, 40 minutes before meals - 15 days, then 7 dragees three times a day - 15 days, followed by 5 dragees three times a day - 30 days. To observe an efficacy of the preparation, a group of 8 people (serum positive, joint form) was established. Control group included 9 people treated with nonsteroidal antirheumatic substances and methotrexate (15 mg). Results were evaluated statistically using nonparametrical criterium by Mann-Whitney.Observed group included 38 patients (84.4%), positive on IgM-RF, and 7 (15.6%) serum negative patients.

Comparison of clinical signs in both groups showed an absence of significant differences (Table II). In serum negative group dominated patients with inner organ damage 85.7%, in serum positive group inner organ damage occured in 57.9% patients.

Presence of antibodies against cardiolipins was tested in serum positive group.
A positive result was obtained in 24 patients (63.2%). In 17 patients (70.8%) inner organ damage developed and only in 7 patients (29.2%) joint form of rheumatic arthritis was diagnosed.

Table I General clinical characterization of patients

Signs	Number of serum positive patients	Number of serum negative patients	Total number of patients
Sex M F	8 30	1 6	9 36
Age 0-40 40-60 more than 60	14 17 7	1 4 2	15 21 9
Degree of activity I II III	5 19 14	- 5 2	5 24 16
Functional I insufficiency II of joints III IV	14 17 7 -	- 4 3 -	14 21 10 -
X-ray stadium I II III IV	4 23 5 6	- 2 4 1	4 25 9 7
Form joint with inner organ damage	16 22	1 6	17 28

Table II Basic clinical signs of joint syndrome

Groups	**Signs of immunological statute**			
	mm/hour	CIC	Titer of antibody against n-DNA, Ig	aCL %
Serum positive (IgM - RF (+)	28.8 ± 0.14*	119.2 ± 0.29*	1.68	63.16
Serum negative (IgM - RF (-))	33.0 ± 0.82*	81.0 ± 1.29*	1.34	85.7

* - statistically significant differences $p < 0.05$
From obtained results it can be concluded that aCL occur in rheumatic arthritis patients sufficiantly frequently - in 66.7% of cases. In patients with inner organ damage aCL were detected more often - in 73.3%. In the groups of serum negative and serum positive patients on IgM -RF, aCL occured with the same frequency - in 83.3% and 70.8%, respectively (Figure 1).
Figure 1: Frequency of an aCL occurance in patients with rheumatic arthritis with different courses.
Analysis of antibody against n-DNA showed that higher titer of the antibody appeared in rheumatic arthritis patients with inner organ damage - 64.3%. When compared serum positive and serum negative groups, antibody against n-DNA was detected in approximately same number of patients - 57.1% and 57.9%, resp. Based on the results of our investigation it could be concluded that inner organ damage (accompanied with an increase of polyclonal hyperglobulinemy, CIC level and of the titer of antibodies against n-DNA and aCL) is considered to be an undesirable symptom caused by a high activity of autoimmune process. Therefore, there is a need for an improvement of the current treatment therapy.
Serum negativity on IgM-RF does not presume a favourable course of rheumatic arthritis with a high titer of antibody against n-DNA, high value of CIC and a presence of aCL. Additionally, in such cases a positivity on IgG or IgA-RF is possible.
Clinical sign analysis of rheumatic arthritis patients, administred with methotrexate and Wobenzym®, gave following results. In patients treated with Wobenzym® a faster reduction of joint swelling, reduction of a degree of morning tightness and a lessening of Li index was observed compared to a control group (Figure 2).

Analysis of immunological statute signs showed that in patients treated with Wobenzym® a more significant lessening of IgM level occured as well as a faster normalization of sedimentation.
CIC degree remained higher (Figure 2).
A faster clinical and immunological remission in patients treated with Wobenzym® and methotrexate enabled to lessen a dosage of methotrexate to 7.5 mg. Two patients voluntarily gave up on methotrexate. During next three months an activation of pathological process did not occur. In the case of one patient an effect of Wobenzym® treatment was negligible, glucocorticoids were therefore administred. Comparison of a treatment efficacy in Wobenzym® group and a control group is shown in Figure 3.
Figure 2: Signs of immunological statute in RA patients treated with and without Wobenzym®.
Figure 3: Effect of Wobenzym® in the rheumatic arthritis treatment.
With regard to a higher CIC values after Wobenzym® administration it is necessary to include a plasmapheresis during first month of treatment. Based on all above mentioned facts it can be concluded that a presence of antibodies against cardiolipins and n-DNA is associated with inner organ damage at IgM-RF serum positive and serum negative rheumatic arthritis. Rheumatic arthritis with inner organ damage, accompanied with an increased titer of antibody against n-DNA, CIC level and a presence of an antibody against cardiolipins, is considered a unfavourable course which needs a therapy improvement.
An increase of n-DNA antibody titer, CIC level and a presence of antibodies against cardiolipins appear to be a more informative signs of an autoimmune process activity in comparison to general clinical observations. Therefore, it is suggested to use these immunological tests for prognosis of a disease course and for control of the therapy efficacy.

New possibilities of basic therapy in patients with rheumatoid arthritis on the basis of systemic enzyme therapy.

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

Wobenzym® (Mucos Pharma, Germany) and NSAIDs (Diclofenac-Sodium) were used in the 2 years-treatment of 15 rheumatoid arthritis (RA) patients, aged 20-55 years, all of them with III disease activity grade, X-ray stage II (Wobenzym® group). The average duration of the disease was 1 to 10 years. 8 patients have been earlier treated by different medication. However, this treatment was found ineffective and further intake of this medication was, therefore, stopped. Control group included 20 patients which received a gold derivate Tauredon as a basic medication (intramuscularly, usual administration scheme). Both groups were comparable by the age, sex, and the main clinical and laboratory parameters. At the beginning of the treatment corticosteroid hormones at the dose of 60-120 mg were intravenously administered (3-6 injections) to the patients in both groups with high grades of the disease activity. Patients received Wobenzym® at the dose of 7-10 tablets 3x daily for 2-4 weeks and 150-200 mg of Diclofenac-Sodium daily at the beginning of the treatment. When a clear disease activity decrease was observed, the dose level of Diclofenac was reduced to 75-100 mg a day, while that of Wobenzym® to 5 tablets 3 times a day. After the achievement of apparent clinical remission, patients continued a supporting treatment by Wobenzym® at the dose of 25-75 mg daily.
Widely used criteria of RA patient's clinical and laboratory state were analyzed.
First clear signs of RA remission appeared in the first (Wobenzym) group after 2-3 months in comparison to 3-4 months in control group. By the 6th month of treatment the apparent clinical remission was achieved in 80% of patients in Wobenzym® group and in about 70% of patients in control group. During second year of observation, an exacerbation of the disease was seen in 2 patients. They were, therefore, additionally treated with Methotrexate.
As evidenced by the data presented, Wobenzym® can be successfully used in the treatment of RA. Systemic enzyme therapy can be combined with corticosteroids, cytostatic immunosuppressors, gold derivates, and NSAIDs.

Wogenzym® in the Treatment of Patients with Juvenile Chronic Arthritis.

Shaivok A.V., Movsisyan G.R., Stolyarova A.V. Wogenzym® in the Treatment of Patients with Juvenile Chronic Arthritis. INt. J. Immunotherapy XIII (3/4) 93-96 (1997).

Summary: Ten children (five boys and five girls, aged 2 through 15) suffering from juvenile chronic arthritis (JCA) were enrolled in the study. All patients received oral Wobenzym® in an open six-month trial. Articular signs and extra-articular manifestations improved in the majority of the children. The experimental drug revealed its therapeutic potential beginning with 4-5 months of treatment. Enzyme therapy appears to be able to limit the use of corticosteroids in some JCA patients. No side effects were observed. Only two children experienced a relapse in the more than 2 years of follow-up exams.

Using of systemic enzymotherapy for treatment of rheumatoid arthritis.

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.

We applied the drug WOBENZYM® (MUCOS Pharma Gmbh & Co., Germany) in the complex treatment of 25 rheumatoid arthritis (RA) patients (mean age 62,1+4,4 years), which formed the basic group (BG), parallel with NSAIDs. In 27 patients of the control group (CG) there were used only NSAIDs. The both groups were comparable by the age, severity of their disease, and accompanying diseases.

The WOBENZYM® was given during 30 days, at the dose of 10 tablets 3 times a day.

The treatment efficacy was estimated by the data of clinical, laboratory and instrumental findings.

The intensity of pain syndrome (by 10-scale) reduced in pts of BG from 6,85±0,28 to 2,80+0,19 units /u./ ($p<0,01$), while in pts of CG from 7,04±0,26 to 3,87±0,24 ($p<0,01$), but this reduction was more pronounced in pts of BG ($p<0,01$).

Pain reduction by 50% was observed in 85% of BG but only in 39.1% of CG pts ($p<0.05$). Patient self-evaluation of treatment efficacy coincided with physician evaluation in 87.5% of BG pts, while in CG -68% ($p<0.05$). There was observed positive dynamics of Stanford form indices: from 31.2±3.5 to 22,1±3,4 in the BG ($p<0,05$), while in the CG changes were insignificant. Also we have observed increase of hand strength in BG and CG by 4,52±0,86 kg and 2,27±0,51 kg, accordingly ($p<0,05$). We have not observed adverse reactions in BG, while in 20% of CG pts ($p<0.01$). By infrared thermography data resumption of inflammatory process, or its essential reduction was stated, ESR also decreased ($p<0.05$).

Thus WOBENZYM® application in complex treatment of RA pts permits to get effective curative results at absence of indesirable effects.

Our experience with Wobenzym® in the treatment of patients with rheumatoid and psoriatic arthritis.

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

Summary:

The objective of the uncontrolled trial was to assess the tolerance and safety of the preparation Wobenzym® in patients with rheumatoid and psoriatic arthritis who had other concurrent anti-inflammatory treatment and to evaluate its position in combined treatment of RA and PsA. The authors added Wobenzym®, 9 to 15 enterosolvent pills per day to anti-inflammatory antirheumatic treatment in 23 patients with RA and 4 patients with PsA because of persisting clinical and laboratory activity. Treatment lasted 16 weeks and more. The evaluation of the effectiveness of Wobenzym® by the physician was as follows: very good 33.3 %, good 54.3 % and unsatisfactory 12.4 %. The evaluation of physical capacity by the patients was as follows: 18 patients (75 %) reported a better physical capacity after Wobenzym® and only 25 % (6) had the same physical capacity. There was no case of deterioration. When evaluating clinical parameters, the authors found after four months of treatment a decline of the morning stiffness ($p < 0.01$) and a better grip strength ($p < 0.05$), reduced articular index and index of incapacity according to HAQ, which however was not statistically significant.

The authors recorded a decline of FW the CRP and CIK concentration ($p < 0.01$).

The concentration of alpha-2 macroglobulin, alpha-1 antitrypsin, haemoglobin and amylase values did not change significantly during treatment. The trial confirmed the favourable effect of Wobenzym® on the rheumatic process, good tolerance and safety of treatment in patients with rheumatoid diseases even in case of polytherapy.

Key words: Wobenzym® - enzyme therapy - rheumatoid arthritis - psoriatic arthritis.

Basic treatment of rheumatoid arthritis: new approaches.

Kovalenko V.N., Golovkov Y. Z. Basic treatment of rheumatoid arthritis: new approaches. Revmatology in Europe 1997, Vol. 26, Suppl. 2, Abst. 446.

Abstract: We applied the drug WOBENZYM® (MUCOS Pharma GmbH & Co., Germany) in the complex treatment of 21 rheumatoid arthritis (RA) patients (mean age 41,1 ± 6,4 years), which formed the basic group (BG), parallel with NSAIDs. In 27 patients of the control group (CG) there were used only NSAIDs.

The both groups were comparable by the age, severity of their disease, and accompanying diseases.

The WOBENZYM® was given during 1 year, at the dose of 15 tablets a day. The treatment efficacy was estimated by the data of clinical, laboratory and instrumental findings, every month. The intensity of pain syndrome reduced in pts of BG from 6,85 ± 0,28 to 2,8 ± 0,19 /points/ ($p<0,01$), while in pts of CG from 7,04 ± 0,26 to 3,87 ± 0,24 /points/ ($p<0,01$), but this reduction was more pronounced in pts of BG ($p<0,01$).

Pain reduction by 50 % was observed in 85 % of BG but only in 39.1 % of CG pts.

(p<0.05). Patient self-evaluation of treatment efficacy coincided with physician evalutation in 87.5 % of BG pts, while in CG – 68 % (p<0.05). There was observed positive dynamics of Stanford form indices: from 31.2 ± 3.5 (units) to 22.1 ± 3,4 in the BG (p<0,05), while in the CG changes were insignificant. Also we have observed increase of hand strength in BG and CG by 4.52 ± 0.86 kg and 2.27 ± 0,51 kg accordingly (p<0,05). We have not observed adverse reactions in BG, while in 20 % of CG pts. (p<0.01). By infrared thermography data resumption of inflammatory process, or its essential reduction was stated, ESR also decreased (p<0.05).
As evidenced by the data presented, WOBENZYM® application in treatment of RA pts permits to effective curative results at absence of adverse reactions.

SPORTS MEDICINE

There are a number of ways that athletes benefit from regular use of Wobenzym® N. The first would be the ability of Wobenzym® N to improve athletic performance by decreasing the inflammatory consequences of that intense physical activity brings about. While the demands of athletic performance tend to improve physical health and cumulatively improve further athletic performance, over training and excessive strain leads to tissue damage with the undesirable consequence of inflammation.
Most of us have experienced the increased achiness that is common after exercise – sometimes it shows up a couple of days after the workout. This represents a degree of inflammation that the body has to recover from.
Think of this a micro-trauma. There is not a bruise, sprain or broken bone, but there is inflammation. Now, as far as the body is concerned, inflammation is inflammation – so the body's resources are being used to react to that inflammation. Specifically; cytokines – those inflammation promoting molecules we have talked about – are increased after intense physical exercise.
As we discussed earlier, Wobenzym® N decreases pro-inflammatory cytokines. As such, it shortens the duration of post exercise inflammation.
The excellent results have been observed in athletes using Wobenzym® N can be explained by its ability to interfere with the inflammation caused by athletic micro-trauma. In this fashion, it improves recovery time.
As recent as February 2014 a study involving 160 healhty marathon runners concluded; "that marathon-induced inflammatory perturbations and the incidence of subsequent URTI, muscular damage, and changes of hemostasis can be positively influenced by the anti-edematous, anti-inflammatory, antioxidant, and fibrinolytic effects of oral hydrolytic enzymes and flavonoids (Wobenzym)." The abstract of that study is included below. At the end of the study you will find a hyperlink that will take you to the full text of the study.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Trauma, Surgery, Sports Medicine & Wobenzym®

What the literature says about Wobenzym® and SPORTS MEDICINE

BMC Sports Sci Med Rehabil. 2014 Feb 22;6(1):8. doi: 10.1186/2052-1847-6-8.

The effects of oral hydrolytic enzymes and flavonoids on inflammatory markers and coagulation after marathon running: study protocol for a randomized, double-blind, placebo-controlled trial.

Grabs V, Nieman DC, Haller B, Halle M, Scherr J. The effects of oral hydrolytic enzymes and flavonoids on inflammatory markers and coagulation after marathon running: study protocol for a randomized, double-blind, placebo-controlled trial. BMC Sports Sci Med Rehabil. 2014 Feb 22;6(1):8. doi: 10.1186/2052-1847-6-8.

BACKGROUND: Regular moderate intensity physical activity positively influences the immune system with a lower incidence of upper respiratory tract infections (URTI) and lower levels of pro-inflammatory markers. However, marathon running due to its strenuous and prolonged nature results in immune perturbations with a major increase in pro-inflammatory markers and subsequent increased incidence of URTI. Furthermore, marathon running results in muscle damage and changes in hemostasis that promote a pro-thrombotic state.Naturally occurring hydrolytic enzymes and flavonoids have antioxidant, anti-inflammatory and fibrinolytic effects, and may serve as countermeasures to exercise-induced inflammation, immune dysfunction and URTI.The aim of this study is to determine whether the ingestion of oral

hydrolytic enzymes and flavonoids before and after a marathon attenuates post-race muscle damage and inflammation, counters pro-thrombotic changes in hemostasis and decreases URTI incidence.
METHODS/DESIGN: The Enzy-MagIC-study (Enzymes, Marathon runninG, Inflammation, Coagulation) is a randomized, double-blind, placebo-controlled, monocenter phase I trial. 160 healthy males (age 20-65 years) will be randomized to receive either placebo or treatment (Wobenzym®, MUCOS Pharma, Berlin, Germany) which contains the hydrolytic enzymes (bromelain, trypsin) and the flavonoid rutoside. One week before the marathon race, participants will begin daily ingestion of the investigational product (3×4 tablets). Intake will be continued for two weeks after the race (3×2 tablets per day). Clinical and laboratory measures will be collected 5-weeks and 1-week before the race, and immediately-, 24-h, 72-h, and 2 weeks after the race. The primary endpoint is the influence of the treatment on the pre-to-post marathon race plasma concentration change of the inflammatory marker interleukin-6 (IL-6). Secondary endpoints include the effect of treatment on salivary IgA concentration and the frequency of upper respiratory tract infections (URTI) for two weeks post-marathon as determined by the Wisconsin Upper Respiratory Symptom Survey (WURSS-24). Furthermore, changes of muscular and rheological parameters will be measured before and after the marathon race. DISCUSSION: We hypothesize that marathon-induced inflammatory perturbations and the incidence of subsequent URTI, muscular damage, and changes of hemostasis can be positively influenced by the anti-edematous, anti-inflammatory, antioxidant, and fibrinolytic effects of oral hydrolytic enzymes and flavonoids (Wobenzym).
TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT01916408.
PMID: 24559067 [PubMed]
PMCID: PMC3945524 (Full Text)

Physical activity and immune system. Systemic enzyme therapy in prevention and treatment.

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

Summary: Besides serious infections, injuries, burns and irradiation, stress is also provoked by a strong physical tension, excessive training and heavy competition rate - factors of professional sporting activity. An important consequence of stress is on affliction of the immune system, its factors and functions, leading secondarily to a decrease of antiinfectious resistance and antitumor surveillance.
While experimental as well as medical experience indicate that regular exercise and recreation sport affects immune system and its function favourably, overtraining, and excessive strain lead to its damage with undesirable consequences. A higher sensitivity to infections is the most prominent: several small-range epidemics have been announced. The paper summarizes main information about changes in the immune system in professionals accomplishing demanding sports - marathon runners, karatists, skiers, cyclists and others. The immune cells (granulocytes, lymphocytes, monocytes, NK) react after an early temporal mobilization with a decline in numbers as well as in functional activities. Similarly, blood levels of immunoglobulins (notably IgA) tend (after a short-time increase) to fall down, often for prolonged time period; the same applies to factors of natural immunity. As underlying mechanisms of these effects there are stress-mediated disturbances of homeostasis, overproduction of some cytokines, adhesive molecules, and toxic radicals.
Among preventive and therapeutic procedures, the attention is paid mainly to combination of proteolytic enzymes. Surprisingly excellent practical results may be satisfactorily explained by selective interferences of enzymes with the pathophysiologic mechanisms of inflammation and by their complex immunomodulatory (immunonormalizing) effects.
Key words: sport, stress, disturbance of immunity, systemic enzyme therapy.

Prophylactic administration of Wobenzym® to reduce consequences of sports injuries in karate fighters.

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.

In a double blind, placebo controlled, randomised clinical trial the efficacy and tolerance of WOBENZYM® adminstration was proved to reduce the consequences of sports injuries in top sportsmen.
20 karate fighters, aged between 13 and 21 years, who underwent a regular training, were included into the trial. 10 volunteers received in the Phase I Wobenzym® tablets and in the Phase II placebo, whereas other 10 sportsmen received in the Phase I placebo and in the Phase II Wobenzym®.
Main evaluation criteria were training absence and absence at work or at school.
Other criteria were duration of hematomas, edema, rest pain, pain on movement, pain on pressure, restricted motility and general inflammatory reactions.
Frequency as well as severity of symptoms were comparable in both groups.

However, their duration was statistically significantly shorter under Wobenzym® treatment. Evaluation of main criteria was statistically significantly better in the enzyme group (training absence 2.2 days compared to 9.5 days in the placebo group, p = 2.87 x 10-6; absence at work or at school 0.2 days compared to 1.8 days, p = 0.024). Evaluation of all other criteria showed statistically significantly better result in the enzyme group as compared to the placebo group (p < 0.001). One case of adverse events was reported in the enzyme group: a slight diarrhea which lasted for five days and did not require any changes of the therapy. There was a possible association with Wobenzym® treatment.
In the study it has been proven that prophylactic administration of Wobenzym® (3x5 tablets daily) in top sportsmen showing a higher risk of injury significantly reduces duration of injury symptoms and training and work absence as a consequence of such injuries.

A double blind, randomised, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes.

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.

OBJECTIVE: To compare the effectiveness and safety of the triple combinationPhlogenzym (rutoside, bromelain, and trypsin) with double combinations, thesingle substances, and placebo. DESIGN: Multinational, multicentre, double blind, randomised, parallel group design with eight groups structured according to afactorial design. SETTING: Orthopaedic surgery and emergency departments in 27European hospitals. PARTICIPANTS: A total of 721 patients aged 16-53 yearspresenting with acute unilateral sprain of the lateral ankle joint. PRIMARYEFFICACY CRITERIA: (a) Pain on walking one or two steps, as defined by thepatient on a visual analogue scale. (b) The range of motion, as measured by theinvestigator and expressed as a sum of flexion and extension. (c) The volume ofthe injured ankle measured with a volometer. RESULTS: At the primary end point atseven days, the greatest reduction in pain was in the bromelain/trypsin group (73.7%). The Phlogenzym group showed a median reduction of 60.3%, and the placebogroup showed a median reduction of 73.3%. The largest increase in range of motion (median) was in the placebo group (60% change from baseline). The Phlogenzymgroup showed a median increase of 42.9%. The biggest decrease in swelling was in the trypsin group (3.9% change from baseline). The Phlogenzym group showed a-2.30% change from baseline and the placebo group a -2.90% change. In thesubgroup analysis of patients who did not use a Caligamed brace, Phlogenzym wassuperior to placebo for the summarising directional test of the primary efficacy criteria (MW = 0.621; LB-CI 0.496; p = 0.029; one sided Wei-Lachin procedure). The vast majority of doctors and patients rated the tolerability of alltreatments tested as very good or at least good.
CONCLUSIONS: Phlogenzym was not found to be superior to the three two-drug combinations, the three singlesubstances, or placebo for treatment of patients with acute unilateral sprain of the lateral ankle joint. The small subgroup of patients treated without thesupport of a Caligamed brace showed evidence of superiority of Phlogenzym overplacebo. Further research is warranted to study this effect of Phlogenzym inpatients treated without ankle support.
External Link: PMID: 15273178

Physical activity and immune system. Systemic enzyme therapy in prevention and treatment.

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

Summary: Besides serious infections, injuries, burns and irradiation, stress is also provoked by a strong physical tension, excessive training and heavy competition rate - factors of professional sporting activity. An important consequence of stress is on affliction of the immune system, its factors and functions, leading secondarily to a decrease of antiinfectious resistance and antitumor surveillance.
While experimental as well as medical experience indicate that regular exercise and recreation sport affects immune system and its function favourably, overtraining, and excessive strain lead to its damage with undesirable consequences. A higher sensitivity to infections is the most prominent: several small-range epidemics have been announced. The paper summarizes main information about changes in the immune system in professionals accomplishing demanding sports - marathon runners, karatists, skiers, cyclists and others. The immune cells (granulocytes, lymphocytes, monocytes, NK) react after an early temporal mobilization with a decline in numbers as well as in functional activities. Similarly, blood levels of immunoglobulins (notably IgA) tend (after a short-time increase) to fall down, often for prolonged time period; the same applies to factors of natural immunity. As underlying mechanisms of these effects there are stress-mediated disturbances of homeostasis, overproduction of some cytokines, adhesive molecules, and toxic radicals.

Among preventive and therapeutic procedures, the attention is paid mainly to combination of proteolytic enzymes. Surprisingly excellent practical results may be satisfactorily explained by selective interferences of enzymes with the pathophysiologic mechanisms of inflammation and by their complex immunomodulatory (immunonormalizing) effects.
Key words: sport, stress, disturbance of immunity, systemic enzyme therapy.

Use of systemic enzyme therapy in the treatment of hand injuries and their consequences.

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

Wobenzym® was administered to the 3 groups of patients (total 52) with various hand traumas:

- Consequences of traumas which needed reconstructive surgery – 15 patients
- Acute hand traumas – 27 patients
- Hand diseases – 10 patients

Wobenzym® was administered according to the standard scheme – 7-10 dragees 3 times a day.
Patients in the 1st group were treated preoperatively (7 days before surgery) and subsequently over 12 days postoperatively. Preoperative treatment showed a positive influence on edema and pain syndrome during a postoperative period.
In Wobenzym-treated patients, edema decreased during 7 preoperative days to 27% (in comparison to 53% in the control group). During early postoperative period edema increased to approx. 60% of the initial condition (compared to the 100% in the control group). Within 12 days after surgery, edema decreased to 7% of the initial condition (19% in the control group). A fast regression of pain syndrome in the Wobenzym-treated patients enabled a discontinuation of analgesic drugs from 2-3 days after surgery.
Patients in the 2nd group were treated with Wobenzym® for 1-month (longer treatment because of trauma severity). Characteristics of edema and pain syndrome development were similar to that of the 1st group.
Patients in the 3rd group were treated with Wobenzym® for 2-3 months. A salutary effect of enzyme therapy in combination with anti-edematous and analgesic drugs occurred during II-III weeks of treatment. Wobenzym® treatment led to a significant decrease of CRP and sedimentation.
Wobenzym® was well tolerated by most of the patients. Side-effects occurred in 2 patients and disappeared after dose lowering.

TENDONITIS

On August 15th, 2009, The American College of Rheumatology published a study by Szczurko, Cooley, Mills, Zhou, Perry and Seely in Arthritis & Rheumatism titled; *Naturopathic Treatment of Rotator Cuff Tendinitis Among Canadian Postal Workers: A Randomized Controlled Trial*.
The study showed a significant decrease in shoulder pain and disability within the group that received the Wobenzym® PS formulation (which is known as Phlogenzym® in the study and other parts of the world). The placebo group showed only 18% decrease in pain and disability, compared to the treated group which showed 54.5% decrease in pain and disability. The treated group also received dietary counseling and acupuncture. The placebo group also received standardized physical exercises.

Research demonstrates that the **Wobenzym® PS** formulation is effective therapy for shoulder tendonitis

The study showed a significant decrease in shoulder pain and disability within the group that received the Wobenzym® PS formulation (which is known as Phlogenzym® in the study and other parts of the world). The placebo group showed only 18% decrease in pain and disability, compared to the treated group which showed 54.5% decrease in pain and disability. The treated group also received dietary counseling and acupuncture. The placebo group also received standardized physical exercises.
The strength of this article is that it demonstrates the same benefits as seen in an earlier study by Klein, et al, titled: *Phlogenzym® in the Treatment of Periarthritis Humeroscapularis Tendopathica*, as well as the study by Kullich, et al, titled: *Treatment with oral enzymes in painful osteoarthritis of the knee and periarthritis of the*

shoulder. Those study compared the **Wobenzym® PS formulation** (Phlogenzym®) to the NSAID diclofenac and found the enzyme formulation to have "moderate superiority" over diclofenac.
The efficacy of the formulation is due to increased clearance of excessive cytokines. The inflammation in tendinitis it mediated by cytokines, including elevated levels of TGF-beta. [Fu SC, Wang W, Pau HM, Wong YP, Chan KM, Rolf CG. Clin Orthop Relat Res. 2002 Jul; (400):174-83.]
Intestinal absorption of the Phlogenzym®/Wobenzym® PS formulation triggers the formation of TGF-beta binding species of alpha2-macroglobulin in blood, such that high concentrations of TGF-beta are reduced via enhanced clearance of alpha2-macroglobulin-TGF-beta complexes. [Lauer2001]
In the 2009 study, we note that the Phlogenzym®/Wobenzym® PS formulation was used in conjunction with diet and acupuncture. Multimodal therapies are common in both naturopathic and allopathic medicine. The ability to use the formulation as an adjuvant - a substance that significantly improves the effective of other therapies due its synergistic properties, is one of the benefits of the Wobenzym® formulations. The Phlogenzym®/Wobenzym® PS formulation has been used as an adjuvant in the treatment of rheumatoid arthritis. [Mazourov1998]

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Joint Pain & Wobenzym®

What the literature says about Wobenzym® and TENDONITIS

Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial.
Szczurko O, Cooley K, Mills EJ, Zhou Q, Perri D, Seely D. Naturopathic treatment of rotator cuff tendinitis among Canadian postal workers: a randomized controlled trial. Arthritis Rheum. 2009 Aug 15;61(8):1037-45. Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada.
Objective: To explore the effectiveness of naturopathic care (NC) on rotator cuff tendinitis using a prospective randomized clinical trial design.
Methods: Canadian postal workers with rotator cuff tendinitis for a duration of >6 weeks were randomized to receive NC (n = 43) or standardized physical exercises (PEs; n = 42) over 12 weeks. Participants in the NC group received dietary counseling, acupuncture, and Phlogenzym (2 tablets 3 times/day). The PE intervention group received passive, active-assisted, and active range of motion exercises and matched placebo. The primary outcome measure was the Shoulder Pain and Disability Index (SPADI), and secondary outcomes were the pain visual analog scale (VAS), Short Form 36 (SF-36), Measure Yourself Medical Outcomes Profile (MYMOP), and shoulder maximal range of motion. Participants and assessors were blinded to group and placebo allocation.
Results: Seventy-seven participants (87%) completed >or=8 weeks of the trial. Final total SPADI scores decreased by 54.5% ($P < 0.0001$) in the NC group and by 18% ($P = 0.0241$) in the PE group. Between-group differences in changes to SPADI scores showed statistically significant decreases in shoulder pain and disability in the NC group compared with the PE group ($P < 0.0001$). Significant differences between groups were also observed in the pain VAS, MYMOP, SF-36, and shoulder extension, flexion, and abduction, with the NC group showing superiority in each outcome. No serious adverse reactions were observed.
Conclusion: NC and PE provided significant improvements, with greater improvement in shoulder function in the NC group compared with the PE group. Statistically significant improvements in quality of life measures were observed in the NC group as compared with the PE group.
PubMed: 19644905

Phlogenzym® in the Treatment of Periarthritis Humeroscapularis Tendopathica.
(MU-695419). Efficacy and Tolerance.Study No.: MU-695419.
Randomised double-blind study phase III with parallel groups vs. diclofenac according to the guidelines of good clinical practice (GCP). Integrated biometric-medical final report according to ICH E3 guidelines. Primary Investigator: Prim. Univ.-Prof. Gert Klein, M.D. Rehabilitation Center for Rheumatic Diseases and Diseases of the Cardiovascular Systém, Thorerstrasse 26, A-5760 Saalfelden, Austria. Evaluation by: MUCOS Pharma GmbH & Co,

Clinical Research Dpt., Malvenweg 2, D-82538 Geretsried. Report by: PharmaScript, Primelweg 2, D-82538 Geretsried

Summary: This double-blind clinical trial could demonstrate that the therapy of a periarthritis humeroscapularis tendopathica with the proteolytic enzyme preparation Phlogenzym® is at least as successful as with the non-steroidal antiinflammatory drug diclofenac. An even moderate superiority of the enzymes was calculated by the Mann-Whitney statistics.

40 patients with periarthritis were taken into this trial and randomised into two groups. 20 patients received the enzymes (enzyme group) and 20 patients received diclofenac (diclofenac group). The data of all patients was evaluable.

The principal investigator was Prof. Gert Klein, M.D., rehabilitation center of rheumatic diseases and diseases of the cardiovascular system, Ludwig Boltzmann-Institut, Thorerstrasse 26, A5760 Saalfelden, Austria.

As the study had to be performed in a "double-dummy" design, all patients received 2 tablets t.i.d. (i.e. 6 tablets per day) of "enzyme tablets" and 1 capsule b.i.d. (i.e. 2 capsules per day) of "antirheumatic agent". Thus, the patients took either 6 tablets of active Phlogenzym® or 100 mg diclofenac for 3 weeks, depending on the group.

At baseline the patients were comparable with regard to age, sex, weight, height, and the symptoms ($p > 0.05$, Wilcoxon-Mann-Whitney-U-test).

As main endpoint for statistical evaluation the sumscore of the various kinds of pain and dysfunction was defined. As secondary criteria the various kinds of pain, the restricted movement, the amount of analgesic drugs taken and the global judgements by the physician and the patients were evaluated descriptively.

Both the main endpoint (sum score) and the secondary criteria showed statistical equivalence. The Mann-Whitney statistics for the main endpoint has even proven a "moderate" superiority of the enzymes: MW statistics = 0.6405, 90% Cl 0.4675 - 0.8136.

The various kinds of pain and the sum score showed also a better improvement in the patients of the enzyme group than of the diclofenac group.

The global judgement of the efficacy of the drug by the physician in the enzyme group was 1.4 ("very good" to "good") and by the patients 1.5 ("very good" to "good"). In the diclofenac group the physician judged the efficacy of the drug as 1.7 ("very good" to "good") and the patients as 1.9 ("good"). The differences between the groups were not significant ($p > 0.05$).

The tolerance of the drugs was judged by the physician in the enzyme group and in the placebo group as 1.2 ("very good") and by the patients as 1.3 ("very good" to "good"). There were no significant differences between the groups ($p > 0.05$).

Adverse events were documented in three patients in the enzyme group (nausea and vomiting, exanthema of the face, allergic exanthema of both upper arms) and in two patients in the diclofenac group (exanthema of the diclofenac group (exanthema of the face). They started on average after 2.7 days in the enzyme group and after 9.0 days in the diclofenac group. The duration was on average 4.3 days in the enzyme group and 4.0 days in the diclofenac group. They were judged as "mild" to "moderate". In the enzyme group two patients were without sequelae and one patient had moderate sequelae and was in need of ambulatory treatment and in the diclofenac group both patients remained without sequelae. In all cases the patient's outcome was without damage. The frequency of adverse events did not differ significantly ($p = 1.000$).

Treatment with oral enzymes in painful osteoarthritis of the knee and periarthritis of the shoulder

Kullich W.*, Klein G.**. Treatment with oral enzymes in painful osteoarthritis of the knee and periarthritis of the shoulder. Reumatologia 1998, Suppl Vol. XXXVI, Warsaw 1998, Lectures No. 213, pp 111-114. ISSN 0034-6233. 619 KA (19-09-2). * Ludwig Boltzmann Institute for Rehabilitation of Internal Diseases, Saalfelden, Austria. ** Rehabilitation Centre for Rheumatic and Cardiovascular Diseases, Saalfelden, Austria. 2nd Central European Congress of Rheumatology, 13-16 May, 1998, Warsaw, Poland

40 patients with periarthropathia tendopathica simplex, aged between 38 and 68 years, were observed. The patients took double-blind randomized the non-steroidal antiinflammatory drug diclofenac in a dosage of 2 x 50 mg daily or oral enzymes (Phlogenzym®; Mucos Pharma GesmbH., Germany) in a dosage of 3 x 2 enteric coated tablets daily, consisting of 90 mg bromelain, 48 mg trypsin and 100 mg of the flavonoid rutosid which normalizes pathologically increased vessel permeability without inhibiting the endogenous defensive power.

The randomization resulted in a patients group with enzyme treatment of 12 men and 8 women with an average age of 54.5 years and a group with diclofenac treatment of 12 men and 8 women with an average age of 51.9 years.

Examinations were made at the beginning and after 1, 2 and 3 weeks of therapy.

For judgement of efficacy, a sum score of four different types of pain (pain on rest, pain on motion, pain on pressure, night pain) and functional impairment was compared.

In our second study 73 patients (36 male, 37 female; 52.0 + 9.1 years of age) with symptomatic OA of the knee and radiographic evidence of joint space narrowing and osteophyte were recruited. A patient's sum score of the Lequesne's index > 10 was demanded.
The study was performed double-blind randomized with a three weeks medication.
Due to the "double blind" method, 37 patients were treated with 50 mg diclofenac sodium 3 times daily.
(TID) during the first week, followed by a dosage of 50 mg diclofenac sodium twice a day (BID) during week 2 and 3, in order to improve the gastroduodenal tolerance. Those patients additionally got "enzyme placebo" tablets. 36 patients were treated with 2 enzyme tablets TID during the whole period. These tablets were an enteric coated enzyme preparation as mentioned in the former presented study. The "double blind" method required an additional application of "diclofenac placebo" in this group. In both groups the therapy was continued with 2 enzyme tablets TID during the weeks 4-7.

THROMBOPHLEBITIS & POSTTHROMBOPHLEBITIC SYNDROME

A common disease that affects veins is **thrombophlebitis** – which is an inflammation of the veins due to blood clotting. A number of studies show that Wobenzym® is very effective in decreasing the pain, edema and throphic ulcers often seen in thrombophlebitis and post-thrombophlebitis syndrome. The studies show improvement of blood flow with increased blood fibrinolytic activity and inhibited platelet function.
In a randomized double blind phase III clinical trial they noted that after 15 days of treatment, there was a significant difference in favor of the enzyme treatment when pain, redness, swelling and induration (a hardening of the tissue due to swelling and inflammation). We see the same improvement in lymphedema.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Cardiovascular and Lymphatic Systems & Wobenzym®

What the literature says about Wobenzym® and HROMBOPHLEBITIS & POSTTHROMBOPHLEBITIC SYNDROME

Application of Wobenzym® and Phlogenzym to the angiology and vascular surgery.

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. Department of Vascular and Urgent microsurgery of the Tbilisi State Medical Academy for Post-Diploma Education [Abstract in Russian]

In 1997-99 enzymotherapy was used in complex treatment of the 150 patients, which were admitted to the clinic of Vascular and Urgent microsurgery of the Tbilisi First City Hospital. 83 of these patients had disease of venous system, including acute thrombophlebitis and postthrombophlebitic syndrome. We had used enzymotherapy with Wobenzym® and Phlogenzym in such cases and observe decrease of pain, reduction of edema and throphic ulcers. The same drugs were used in the treatment of arterial pathology (in 25 patients) with positive clinical outcomes.
We also used enzymotherapy in treatment of 42 patients with different traumas of the hand. After application of enzymes in such cases, decrease of pain, reduction of edema and improvement of microcirculation of the injured site were observed.
Basing on our experience we conclude, that enzymes, as medical means with high efficacy and practical absence of adverse reactions, must be widely used in the complex treatment of vascular and traumatic disorders.
Key words: enzymotherapy, Wobenzym®, Phlogenzym, vascular and traumatic disorders.

Systemic enzyme therapy of lower limb postphlebitic syndrome.

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. Department of Faculty Surgery, Russian State Medical University, Moscow, Russia [Abstract in Russian and Czech]

Large clinical material (66 patients) and modern diagnostic modalities were used for comparative study of systemic enzyme therapy (Phlogenzym, 2 dragees per 3 times per day for 3 months) and conventional combined therapy of lower limb postphlebitic syndrome. Clinical effect of systemic enzyme therapy was more pronounced (84% for systemic enzyme therapy vs 73% for conventional therapy). Better outcome was provided by significant changes in hemostasis and blood rheological parameters, especially by increased blood fibrinolytic activity and inhibited platelet function. These resulted in facilitation of venous outflow from affected extremity and clinical regression of chronic venous insufficiency.
Key words: systemic & enzyme therapy, postphlebitic syndrome, hemostasis, blood rheology, venous outflow.

Wobenzym® in the treatment of Thrombophlebitis.

Džupina A.[1], Džupinová M.[2] Wobenzym® in the treatment of Thrombophlebitis. Praktická flebologie 1998, Roè. 7, è. 1, str. 28-30 (17-12-3) 1 Internal Department, City Hospital and Clinic, Bardejov, Slovakia; 2 Immunology and Alergology Clinic, City Hospital and Clinic, Bardejov, Slovakia [Czech abstract]

Summary: We would like to emphasize, that Wobenzym® therapy of 46 deep vein thrombosis patients treated for one year led to a disappearing of followed subjective troubles and to the improvement in objective duplex ultrasound findings. These facts allowed us to omit the anticoagulation therapy in 20 patients. In the rest of 26 patients the therapy led to a reduction of the leg edema and to the better centripetal stream monitored by duplex ultrasound as well as to a reduction or vanishing of the subjective troubles of patients. This means better quality of patient`s life. Therapy by proteolytic enzyme preparations in this indication is, in our opinion, very suitable. Its effect is to be verified by more extensive trials with more patients.

Wobenzym® in the Treatment of Acute Thrombophlebitis (MU-693204)

Valery M. Koshkin, M.D., D.M. Sci.Wobenzym® in the Treatment of Acute Thrombophlebitis. PharmaScript, Kathi-Kobus-Steig 1, D-82515 Wolfratshausen, Germany

Summary: In a randomised double blind clinical trial phase III (acc. to German Drug Law) with two parallel groups, it should be demonstrated in patients with thrombo- or varicophlebitis whether the enzyme preparation Wobenzym® reduces pain and edema earlier than a placebo treatment.

119 patients with clinically verified acute thrombophlebitis or varicophlebitis of a superficial vein of the lower extremity were taken into this study. 60 patients received the enzyme preparation and 59 placebo. The data of all patients was evaluable.

Primary investigator was Prof. Valery M. Koshkin, M.D., D.M.Sci., Angiology Laboratory, Department of Surgery, State Medical University of Russia, Leninsky prospect, 8 Ia, Moscow, 117049 - Russia.

The patients received 10 tablets t.i.d. (= 30 tablets per day). The therapy lasted 15 days.

At baseline the patients were comparable with regard to age, sex, height, weight and the symptoms pain, redness, induration, swelling, sum score of the symptoms, length of the inflammatory vascular process and time for refilling of the veins ($p > 0.05$, Wilcoxon-Mann-Whitney-U-test).

The main endpoint for statistical evaluation was the sum score of the symptoms pain, redness, induration and swelling. As secondary criteria the other parameters for evaluation of the efficacy like pain, redness, induration, swelling, length of the inflammatory vascular process, smallest circumference supramalleolar, largest calf circumference, knee circumference, circumference 15 cm above the knee, time for refilling the veins (by light-reflexion-rheography), the result of therapy and the subjective judgement of efficacy by the physician and the patients were evaluated. Other secondary criteria were the laboratory parameters (ESR, white blood cells, platelets, AST, ALT, g-GT), the subjective judgement of tolerante, and adverse events caused by the study therapy.

The main endpoint - the sum score of pain, redness, induration and swelling - showed a statistically significant difference on the 5% level ($p = 0.033$) after 15 days of treatment in favor of the enzyme treatment.

The judgement of the secondary criteria showed statistically significant differences in favor of the enzyme treatment with pain ($p = 0.033$), the length of the inflammatory vascular process ($p = 0.005$) and the time for refilling the veins of the affected leg ($p = 0.005$).

The result of therapy in the enzyme group was on average 2.6 ("good" to "moderate") and therefore some better than in the placebo group with 3.0 ("moderate"), but the difference was not statistically significant ($p > 0.05$). The efficacy of the drug was judged by the physician at the end of therapy in the enzyme group with 2.6 ("good" to "moderate") and in the placebo group with 2.9 ("moderate"). The patients judged the efficacy as 2.6 ("good" to "moderate") in the enzyme group and es 2.8 ("moderate") in the placebo group. The differente between the groups was not statistically significant ($p > 0.05$).

The tolerance of the therapy was judged by the physician in the enzyme group as 1.8 ("good") and in the placebo group as 1.7 ("very good" to "good"). The judgement by the patients was similar: 1.9 ("good") in the enzyme group and 1.8 ("good") in the placebo group. There was no significant difference between the groups ($p > 0.05$).

Adverse events occurred in either group. Three were documented in the enzyme group and four in the placebo group. The difference between the groups was not statistically significant ($p > 0.05$). In the enzyme group there was one thrombosis on the contralateral leg, one deep vein thrombosis of the lower extremity and one acute ileofemoral thrombosis. The onset was on average after 7.0 days and they lasted for 7.3 days. The severity of all adverse events was "moderate" and the cause judged as "unknown". In all three patients the study therapy was stopped and twice a

symptomatic therapy of the adverse events with heparin was necessary. In two patients residual complaints did not arise and the patient's outcome was without damage. In one patient residual complaints without specification were seen, there was a transitory damage. In the placebo group there were dysphagia, nausea and headache. They started on average after 6.8 days, the duration was one day, and they were "moderate". They were caused in one patient by the study drug, and in three cases the cause was unknown. In one patient the therapy was stopped, in one patient no measures were taken, and in two patients a symptomatic therapy of the adverse event with analgesics was necessary. No residual complaints were seen in any case, and all patients outcome was without

URINARY TRACT INFECTIONS

Adding enzyme therapy to the antibiotic therapy dramatically shortens the time that it takes both feel better, and for lab tests to show a decrease in the systemic inflammation that accompanies a urinary tract infection. This has been observed in the recurrent urinary tract infections – which have traditionally been very hard to treat –even with antibiotics and other drugs.

Keep in mind, these recurrent urinary tract infections are notorious for being hard to treat and hard to keep coming back. The fact that we can use Wobenzym® to make antibiotics more effective – and to prevent re-infection – is a very important point.

When we use Wobenzym® to make antibiotic more effective we are using the adjuvant properties of Wobenzym®. An adjuvant is a substance that significantly improves the effective of other therapies that have limited effectiveness. Wobenzym® has been used as an adjuvant to treat a number of inflammatory and infectious diseases. This hold true for not only recurrent urinary tract infections and pyelonephritis, but also for recurrent respiratory tract infections, as well as chronic infections of the reproductive system.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:
Kidney and Bladder Conditions & Wobenzym®

What the literature says about Wobenzym® and URINARY TRACT INFECTIONS

Phlogenzym® in patients with relapsing urinary tract infections.

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

Summary: Efficacy and tolerance of the enzyme combination preparation Phlogenzym® were tested in a randomized double blind clinical phase III (acc. to German drug law) trial with two parallel groups in patients with relapsing urinary tract infections (UTI) as compared with placebo.

Forty (40) patients with the typical symptoms of UTI (as pollakisuria, nycturia, dysuria, imperative strangury, painful micturition and suprapubic pain) were taken into this study.

All 40 patients received an antibacterial therapy during the first week. Twenty (20) patients took the test preparation Phlogenzym® and another 20 patients got placebo: each two tablets t.i.d. of the active or the placebo drug, resp., for three weeks. The data of all 40 patients were evaluable.

The primary investigator was Peter Schlüter. M.D., Gartenstrasse 16, D-69502 Hemsbach, Germany.

At baseline, the groups were comparable with regard to age, sex, height and weight, and the six symptoms of UTI mentioned above ($p > .05$ in Wilcoxon- Mann-Whitney-U-test).

A sum score of the six clinical symptoms was defined as main endpoint for efficacy. Secondary criteria were urinalysis, blood picture and serum diagnosis, and global judgement of efficacy by physician and patients.

The main endpoint "sum score" showed a statistically significant superiority ($p < 0.0001$) in favor of Phlogenzym® at days 3, 7, and 14.

The inflammation was healed in all patients at day 14 in the Phlogenzym® group, whereas some patients still had UTI at day 14 and even day 21 in the placebo group.

Laboratory values from urinalysis, typical for UTI normalized earlier in the Phlogenzym® group, with several significant differences ($p < .05$).

Improvement of ESR and reduction of leucocytes in the blood correlated with the decrease of inflammation.

Physician and patients judged the efficacy of Phlogenzymâ significantly superior to that of placebo ($p < .0001$, and $p = .0002$, resp.).

The tolerance was excellent, as seen from the global judgement of tolerance by physician and patients, as well as from the complete lack of unwanted side effects.

UVEITIS (inflammation of the middle layer of the eye)

When treated with Wobenzym® PS (Phlogenzym), 60% of patients with anterior uveitis were improved within about 17 days. I believe this data can be used to treat posterior uveitis based on the ability of Wobenzym® to decrease TNF-alpha levels (a pro-inflammatory cytokine), and the current trend to use anti-TNF alpha antibodies to treat posterior uveitis. Wobenzym® has shown some effectiveness in treating Behcet's Disease, in which uveitis is a common presentation. Behcet's may cause either anterior uveitis (inflammation in the front of the eye) or posterior uveitis (inflammation in the back of the eye), and sometimes causes both at the same time.

Anterior uveitis results in pain, blurry vision, light sensitivity, tearing, or redness of the eye. Posterior uveitis may be more dangerous and vision–threatening because it often causes fewer symptoms while damaging a crucial part of the eye — the retina.

Please see the **FREQUENTLY ASKED QUESTIONS** section on:

Eyes, Ears, Nose & Throat Conditions & Wobenzym®

What the literature says about Wobenzym® and UVEITIS

Our first experience with utilisation of hydrolytic enzymes in arterior uveitis.

Porubská M. Department of Ophthalmology, Institute of Respiratory Diseases, Nový Smokovec, Slovakia. Rheumatologia 2000, Roč 14, č 2, str. 65-69. (3-14-1)

Summary: Objective: New therapeutic methods with lower adverse effects than those of corticosteroids and immunosuppressive are seeked for in the treatment of anterior uveitis. The aim of the monitoring was assess the efficacy of Wobenzym® and Phlogenzym in the anterior uveitis activity and to compare their therapeutic effect with the effect of high doses of both the system and parabulbar application of corticosteroids and/or immunosuppressives.Methods: A group of 29 hospitalized patients with the high activity of anterior acute and chronic uveitis received enzyme preparations for 8 weeks and paralelly, decrease of inflammatory activity was evaluated.Results: In a group of patients with anterior acute uveitis mostly associated with ankylosing spondylitis, inflammatory cells from the eye anterior chamber in patients treated with hydrolytic enzymes got absorbed on average in 20 days compared to 27 days in the control group. In the patients with chronic anterior uveitis mostly associated with juvenile chronic arthritis all the inflammatory cells in 50 % of the patients treated with Wobenzym® got absorbed on average in 20.3 days, in 60 % of the patients treated with Phlogenzym they got absorbed on average in 17.3 days with the most persisting effect and in the control group in 37 % of 'the patients on average in 30 days. In the patients receiving enzymes. Fibrín and Tyndal got absorbed in 1 day, in the control group in 4-5 days. Conclusion: The results suggest that, utilization of hydrolytic enzymes makes possible to lower the dosage of corticoids and contributes to shorter time needed for inhibition of the uveitis inflammatory activity, important especially in children with JCA. The best results were observed in administration of Phlogenzym.

Key words: hydrolytic enzymes, corticosteroids, anterior chamber, uveitis.

FREQUENTLY ASKED QUESTIONS

The Science behind Systemic Enzyme Support

What is systemic enzyme support?
Systemic enzyme support is a therapy the uses specific enzyme compounds to increase the enzyme levels throughout the body, and improve the function of the various body systems, primarily by modulating, controlling and balancing the inflammatory and oxidative processes that occur throughout the various body systems.
This is important because oxidative stress is a byproduct of normal metabolism, and this oxidative stress can promote inflammation. In addition, inflammation can occur because of various insults to the body, including trauma, infections and even the everyday “wear and tear” that occur with normal activity.
These enzyme compounds – the Wobenzym® formulations - are specific combinations of enzymes in enteric coated tablets that are designed that way to they can be absorbed into the bloodstream and delivered systemically. It is this ability of systemic enzymes to be delivered to the various body systems that distinguishes the Wobenzym® formulations from other enzyme supplements.
So, "systemic enzyme support" describes an approach whereby enzymes are utilized to assist the body's various regulatory and communication systems, specifically the immune system. A balanced immune system is a prerequisite for the condition we all want: good health. In order to make sure that the systemic effect of the enzyme support succeeds, active enzyme molecules must be available in the small intestine for absorption.

How is systemic enzyme support therapy different than the digestive enzymes?
Digestive enzymes are specifically designed to help digestive system break down food more efficiently with enzymes. They are primarily used to help digest proteins – though they can also help digest carbohydrate and fats. Digestive enzymes pretty much stay in the digestive tract are used to strengthen digestive function when the body cannot make enough of its own enzymes to properly digest the food. So, the activity is primarily on digestion.
True – if we improve digestion other parts of the body benefit. But digestive enzymes do not do the same thing that Systemic Enzymes do.
Systemic enzymes are quite different. Systemic enzymes are absorbed into the blood and act primarily on the immune system, and their action is to balance the immune system. This balance is critical because so many health conditions are in part because of abnormal inflammation – inflammation out of control.
We know that inflammation is important – if we are fighting infection – such as a splinter in the hand. We see redness, heat, swelling, and pain, as well as difficulty moving the finger wit with the splinter.
However, when inflammation is out of control – and we see red, hot, swollen, painful, hard to move knees and hands with arthritis, we know it is the immune system that needs to be addressed.
That is what Wobenzym® N does. It is a systemic enzyme formulation that addresses abnormal immune system function and restores balance in the immune system.

How does Wobenzym® N control inflammation?
The key to describe how Wobenzym® controls inflammation would have to be the word – balance. The immune system is very complex – how does it destroy pathogens but not destroy our own tissue? How do we keep it strong enough to protect us? Traditionally, therapies that target the immune system could stimulate it make it more aggressive – such as Echinacea – or it could suppress the immune system – using anti-inflammatory herbs such as Salix alba boswellia or ginger concentrates. Of course, we see this carried to the extreme with powerful chemical antibiotics or with immune-suppressants (prednisone).
Wobenzym® N does not suppress or stimulate the immune system. It balances it. So the immune system can do what it was designed to do.
The immune system is designed to control the infection or trauma, clean up the debris, and set the groundwork for rebuilding healthy tissue.
If we approach arthritis with the intent of suppressing the immune system with prednisone or other immune suppressant then we interfere with the body’s ability to carry out the other duties of the immune system, such as cleaning up the debris and setting the ground work of healing and rebuilding.

What part of the immune system is actually being balanced?
The immune system has its own method of communication. Cells close to infection or trauma or degenerated tissue need to tell other cells that something has to be done. This is done with chemical messengers are protein-like molecules called cytokines. Some cytokines increase inflammation – destroy pathogens or damaged tissue – other cytokines calm down the inflammation. These two groups of cytokines are typically divided into two groups –Th1 and Th2.
Th1 cytokines include cytokines such as Interferon-gamma and Tumor Necrosis Factor-alpha, as well as Interleukin-2, 6 and 12. Th2 cytokines include cytokines such as Interleukin-4, 5 & 10, as well as Tissue Growth Factor-beta. When the two groups are imbalanced we different types of inflammation.

If cytokines are imbalanced, what type of inflammation would we see?
Excessive Th1 can cause an exaggerated response to inflammation such as too many aches and pains with everyday activity, or an excessive amount of inflammation after sports activity – which could cause people to exercise less.
Long term excessive Th1 ultimately lead to destructive immune processes such as autoimmune diseases, including as rheumatoid arthritis, autoimmune thyroid disease, etc.
Excessive Th2 activity can cause the allergy syndromes (atopy) such as asthma, eczema and eyes and nose allergies.
Long term excessive Th2 activity can lead to increased risk of cancer, or conditions that are a result of immune system suppression including frequent infections or increased viral outbreak – such as shingles (herpes zoster).
The unique ability of the Wobenzym® N is best summed up by saying it has the ability to balance the immune system – it restores normal function. It is not control inflammation through immunosuppression. It is not an immune-stimulant. It balances the immune system, so that it can do what it was designed to do.

How does Wobenzym® N balance the cytokines?
By increasing systemic enzyme levels, Wobenzym® N increases the activation of alpha-2-macroglobulin, a protein that is "found abundantly in plasma and interstitial fluids". (Interstitial fluid is the fluid found the cells of the body.
Alpha-2-macroglobulin acts a chaperone to remove excessive cytokines, damaged parts of cells (cellular debris - garbage) and damaged or dangerous protein molecules form the blood.
This protein, called alpha-2-macroglobulin, is typically decreased and is not as activated, with age and with certain diseases, so the body's ability to clean itself of unwanted proteins is diminished. Wobenzym® N activates alpha-2-macroglobulin, and enhances the body's ability to maintain alpha-2-macroglobulin production.
The activated alpha-2-macroglobulin restores normal immune function – allows it to go back to a balanced healthy state.
The relationship between activated alpha-2 macroglobulin and immune system health is critical for prevention and control of both acute and chronic disease.
The ability of Wobenzym® N to restore immune system health - through restoration of normal balanced function – is why Wobenzym® N is so effective in such as wide range of inflammatory conditions.

What does the activated alpha-2-macroglobulin help remove from the blood stream?
In addition to excessive cytokines, activated alpha-2-macroglobulin is able to bind to, and promote the clearance of various antigens such as bacteria, viruses, yeast, pollens and other allergenic substances. Excessive antibodies, such as those seen in autoimmune disease, can also be removed.
Circulating immune complexes (CICs) – which are formed when antigens and antibodies stick together – can be removed. It is important to note that circulating immune complexes may be quite elevated in autoimmune disease and can cause disease when they become imbedded in tissues. CICs are very pro-inflammatory.
As I mentioned, enzyme activated alpha-2 macroglobulin facilitates the removed of cellular debris and damaged proteins. These damaged proteins may be the result of increased oxidative stress, or of glycosylation – the damage caused by excessive blood sugar.
The enzyme activated alpha-2-macroglobulin also facilitates the removal of other proteins such as excessive fibrin, amyloid and C-reactive protein (CRP) by binding to these proteins so they can be eliminated from the circulation.
The net result is an improved removal of the substances that promote inflammation - from both the circulation and the fluid between cells, by binding them to the activated alpha-2-macroglobulin.

How is the activated alpha-2-macroglobulin with all of the bound cytokines, antigens and proteins removed from the circulation?

The enzyme activated a2M, with the bound cytokines, antigens and proteins actually initiates its own removal (and the removal of the inflammatory substances) from the blood stream and uptake by macrophages. These macrophages are already in the circulatory system and in the spaces between cells. The enzyme activated alpha 2-macroglobulin promote macrophage locomotion and chemotaxis (movement initiated by a chemical message). The enzyme activated alpha 2-macroglobulin- complexes are cleared from the circulation very quickly by macrophages.
The macrophages engulf, and then digest the cellular debris, excessive cytokines, bacteria, yeast, viruses, pollen, other allergens, excessive antibodies, excessive circulating immune complexes & other unwanted proteins that have been captured by the activated alph-2-macroglobulin.
It is important to understand that if the cellular debris, excessive cytokines, bacteria, yeast, viruses, pollen, other allergens, excessive antibodies and the excessive circulating immune complexes were allowed to stay in the circulatory system, and allowed to become attached to tissues throughout the body we would see increased inflammation with a decreased function and decreased health of various body systems. These imbalanced substances promote inflammation and are involved with the pathogenesis – with the actual beginning – as well as the progression - of most diseases.

Noting that Wobenzym® formulation balance the immune system, what other body systems are affected by taking these systemic enzyme formulations?
They will see that by balancing the immune system – and the controlling of inappropriate inflammation that can affect every system in the body - they can improve the function of any body system that has not been working properly due to inflammation.
Now keep in mind; inflammation can adversely affect every system in the body: the cardiovascular system, the nervous system, the musculoskeletal system, the endocrine system, the urinary system, and so on.
Any system that can be damaged by inflammation – and that is every system – can function better when the inflammation is controlled.
Because Wobenzym® induces the anti-inflammatory affect on the whole body – because it supports the enzyme activated clearing of inflammatory substances - its actions are appropriately called systemic.
The medical science is quite clear: by controlling systemic inflammation, we improve the function of every body system. And by improving the function of every body system Wobenzym® is used to treat quite a large number of diseases and health conditions.
Again, the science shows this – with hundreds of published studies that were done on the Wobenzym® formulations.

Cardiovascular and Lymphatic Systems & Wobenzym®

What heart conditions has Wobenzym® been used on?
When Wobenzym® was added to the treatment of angina pectoris (chest pain due to heart problems), the frequency and intensity of angina attacks were reduced and tolerance to physical load was increased. A drop in pro-inflammatory cytokine levels was also noted.
Patients who have suffered a myocardial infarction – a heart attack – had lower risk of re-infarction when they were given Wobenzym®. Normalization of lymphocytes, and a lowering of circulating immune complexes was observed.
Wobenzym® also decreased cholesterol an average of 24% after one month of therapy. It also lowered the levels of atherogenic lipoproteins as well as inflammatory markers associated with atherosclerosis.
It is important to note that in addition to lowering excessive lipids, controlling inflammation in cardiovascular disease is also recognized as an important benefit of systemic enzyme support.

In addition to controlling the inflammation that causes heart disease, can Wobenzym® lower cholesterol?
One study showed that in patients who had suffered a myocardial infarction, cholesterol dropped 12% and lipoproteins drops 16% after taking 9 Wobenzym® tablets a day for 10 days. A second group in the same study had a 24% drop of cholesterol and 31% drop of lipoproteins within one month at the same dosage. The researched also noted that the immune status of myocardial infarction (MI) patients is significantly impaired and that Wobenzym® had an immunonormalizing affect.
A parallel study of myocardial infarction patients and two groups of rabbits reported a “significant decrease of cholesterol level” in both the clinical and the experimental studies. They concluded that “it can be recommended to use Wobenzym® in complex treatment of myocardial infarction patients to reduce risk factors of reinfarction.”

A 2001 study tracked 52 patients taking Wobenzym® for 6 months. They also noted an improvement lipid levels. They also noted an improvement in cytokine levels, and concluded in postmyocardial infarction patients Wobenzym® helped improve the biochemical and immune abnormalities.
It is also notable that patients with autoimmune thyroid disease experienced lower cholesterol and triglyceride levels after being treated with Wobenzym®. Now this may be because their anti-thyroid antibody levels had dropped with Wobenzym® therapy, but it is still notable that cholesterol levels are improved in these patients.
I should also point out that improved cholesterol levels are also observed in chronic levier disease patients after they were treated with Wobenzym®

Can Wobenzym® be taken if people are on other medication for their heart disease?
The studies are telling use yes. In some studies, the patients were also on beta-blockers, nitrates, aspirin and ACE inhibitors. Learn more in the section on myocardial infarction
I should point out that since Wobenzym® has a fibrinolytic action – it decreased blot clots – patients taking powerful anticoagulants such a warfarin (trade name Coumadin) or other prescription blood thinners, should not take Wobenzym®, unless under the supervision of a physician that is experienced in systemic enzyme therapy and coagulation management. A study reports it is safe to take with aspirin.

How does Wobenzym® help other parts of the circulatory system, such as the veins?
A common disease that affects veins is thrombophlebitis – which is an inflammation of the veins due to blood clotting. A number of studies show that Wobenzym® is very effective in decreasing the pain, edema and throphic ulcers often seen in thrombophlebitis and post-thrombophlebitis syndrome. The studies show improvement of blood flow with increased blood fibrinolytic activity and inhibited platelet function.
In a randomized double blind phase III clinical trial they noted that after 15 days of treatment, there was a significant difference in favor of the enzyme treatment when pain, redness, swelling and induration (a hardening of the tissue due to swelling and inflammation). We see the same improvement in lymphedema.

How is lymphedema related to the circulatory system, and how does Wobenzym® improve this condition?
Lymph is the fluid that is formed from the fluids that bathe and surround the cells in the tissues of the body. This fluid is carried back to the circulation through lymphatic vessels. When these vessels do not drain properly the fluid collects in the tissues causing edema, or more specifically lymphedema.
So, lymphedema is the swelling of tissue due to retention of fluid in the lymph vessels. Lymphedema can have many causes, affects 175 million people worldwide, and can lead to infection, pain, severe disability and even increased risk of cancer. It is a disorder which is traditionally very difficult to treat. So you can realize why I was pleased to read the studies that were done with Wobenzym® treating lymphedema.
What I found, was that a number of studies specifically looked at the affect that Wobenzym® has on lymphedema. It was noted that there was significant reduction in pain and swelling with a lower risk of infections. Even primary lymphedema (hereditary lymphedema) showed significant improvement.

Joint Pain & Wobenzym®

Is Wobenzym® a pain reliever?
Pain reduction has been well documented in various conditions, including rheumatic joint disease. These analgesic effects are based on the inhibition of inflammation as well as the direct influence on the nociceptors – the nerve cell endings that initiate the sensation of pain. This ability to address both the source of the pain – swelling and inflammation – and to actually relieve the pain by decreasing the noxious stimuli to pain receptors – so that the pain signal is diminished, makes Wobenzym® a very good choice for pain management, especially when it comes to joint pain.

How does this apply to joint pain, which is one of the most common causes of pain?
There are different reasons for joint pain – different types of arthritis. Wobenzym® has been shown to be effective in treating all forms of arthritis. A point to remember is the word “arthritis” literally means “joint inflammation”. Yes, pain is often involved, and we could use the term “arthralgia” which means “joint pain”, but the root cause of that pain is inflammation, so our goal is to address the inflammation, which will also relieve the pain. Systemic enzyme support is

effective in treating joint pain because of its ability to control the destructive inflammatory processes involved in the various forms of arthritis.
The different forms of arthritis include osteoarthritis, rheumatoid arthritis, as well as psoriatic arthritis, juvenile chronic arthritis and even gouty arthritis.
Considering patients with osteoarthritis, also known as degenerative joint disease: A 2006 six-week phase III, randomized, double blind, parallel group study compared systemic enzyme support with diclofenac the generic name for a nonsteroidal anti-inflammatory drug that is widely used to treat arthritis. Keep in mind that diclofenac can increase the risk of life-threatening heart or circulation problems, including heart attack or stroke – and the longer it is used, the greater the risk. Contrast that to those studies that conclude that Wobenzym® reduced the risk if myocardial infarction.
Now, consider this: the 2006 study found systemic enzymes were as effective as diclofenac – and noted that the systemic enzymes were better tolerated.
A 2004 randomized, double-blind, parallel group trial by a different group of researchers came to the same conclusion. Within the six-week observation period, they noted that that systemic enzyme support "can be considered as an effective and safe alternative to NSAIDs such as diclofenac in the treatment of painful episodes of OA of the knee."
And before that, a 2001 randomized, controlled, single-blind study of seven weeks duration found that systemic enzyme support "is as efficacious and well tolerated as diclofenac" in the management of active osteoarthritis.
A number of studies conclude that Wobenzym® is an effective and safe alternative to NSAIDS in the treatment of painful episodes of osteoarthritis of the knee and hip.
So, we see that systemic enzyme support is as effective as – and in my opinion safer than - nonsteroidal anti-inflammatory drugs for the management of osteoarthritis. We see similar results for rheumatoid arthritis and other forms of arthritis.

How is rheumatoid arthritis different that osteoarthritis?
As you may know, rheumatoid arthritis (often called RA) is a chronic systemic inflammatory disorder that primarily attacks the joints – although other tissues may be inflamed as well. Rheumatoid arthritis is an autoimmune disease, so it is often treated with high dosages of steroid hormones or other powerful drugs like methotrexate, or gold salts, or high dosage NSAIDs.
Because rheumatoid arthritis is an autoimmune disease there are increased amounts antibodies, such as Rheumatoid Factor and IgG-RF. This can result in increased circulating immune complexes, which, as we mentioned earlier, are quite pro-inflammatory. We also see increased levels of proinflammatory cytokines such as TFN-alpha (tissue necrosis factor – which, as the name implies, promotes destruction of tissue). As you would expect, there are also increased levels of C-reactive protein.
In contrast to osteoarthritis – which is a degenerative process, rheumatoid arthritis is an actively destructive process.

How does Wobenzym® affect the destructive process in rheumatoid arthritis?
The studies show that systemic enzyme support is able to arrest the inflammatory process, and relieve the pain, swelling, and redness of affected joints. A 2001 study reported that in most patients that were "definite signs of rheumatoid arthritis remission appear at the end of the first month" in patients taking 30 Wobenzym® tablets a day.
An earlier study revealed had patients taking 7 to 10 Wobenzym® tablets, 3 times a day for 2 to 4 weeks, and then lowered it to 5 tablets 3 times a day and monitored them for two years. Even at that lower dosage apparent clinical remission was achieved in 80% of patients by the 6th month of treatment.
There is more detailed information about dosing in another segment of this book, but this is a good time to point out that in aggressive and destructive inflammatory conditions like rheumatoid arthritis, we typically see results at the therapy dosage of about 30 Wobenzym® N tablets a day.
In addition to improvement of pain and other symptoms, we see changes in lab results that monitor systemic inflammation. Another study showed that from 15 to 30 tablets of Wobenzym® a day resulted in greater reduction of C-reactive protein, circulating immune complexes and pro-inflammatory cytokines, including TNF-alpha.
In fact, in patients treated with Wobenzym®, the TNF-alpha levels were 40% - less than half – of the levels seen in untreated patients.
Just as we saw in osteoarthritis, Wobenzym® protects and preserves joint cartilage significantly better than NSAIDs in rheumatoid arthritis50-60.

What other types of arthritis can benefit from using Wobenzym®?
Juvenile chronic arthritis is a group of systemic inflammatory disorders affecting children below the age of 16 years. Because of its inflammatory nature it is often compared to the rheumatoid arthritis seen in adults. It is a relatively rare condition (9 – 25 per 100, 000) which affects girls 2 to 3 times more often than boys. A small study including both boys and girls revealed therapeutic benefits with 4 to 5 months. No side effects were observed. Only two children experienced a relapse in the more than 2 years of follow-up exams. The addition of systemic enzyme supports 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.
Psoriatic arthritis is a type of inflammatory arthritis that affects about 10 to 30% of people who have psoriasis. A small study showed improvement at about 4 months as well. Now what is interesting, is they only used 9 to 15 tablets of Wobenzym® a day, and patients with rheumatoid arthritis in the same study also required 4 months to improve. So again, in aggressive and destructive inflammatory conditions, I always advise a therapeutic dosage of 30 tablets a day.
Gout is a form of arthritis that affects mostly middle-aged men and postmenopausal women. After 3 weeks of adding Wobenzym® to conventional gout therapy, they saw an improvement of 94.1% compared to only 47.3% with only conventional therapy.
So when you look at the research, you could say that Wobenzym® is a good therapy for all forms of arthritis including osteoarthritis, rheumatoid arthritis, as well as psoriatic arthritis, juvenile chronic arthritis and even gouty arthritis.

If someone is already taking some type of medication for their arthritis, can they still take Wobenzym®?
I would have to say yes. There have been Wobenzym® studies with patients already taking non-steroidal anti-inflammatory drugs (NSAID) such as diclofenac sodium, movalis, phelden, or indomethacin. Some of the studies also included patients taking allopurinol or methotrexate in addition to the NSAID.
Learn more at: Rheumatoid Arthritis
These studies show that Wobenzym® N is actually able to improve the effectiveness of other mediations that are not working. This is important because when the routine medications for severe diseases failt to work, the patient more likely to be put at risk by trying to using stronger mediations with more severe side effects. While it is nice to know that Wobenzym® N can make other drugs work better, we should keep our eyes on the other studies that show Wobenzym® N actually working as good as the drugs.

How effective is Wobenzym® for treating tendonitis?
In treating tendonitis of the shoulder, Wobenzym® PS significantly decreases both shoulder pain and disability within the patients receiving the formulation.

Trauma, Surgery, Sports Medicine & Wobenzym®

How does Wobenzym® N benefit athletes?
There are a number of ways that athletes benefit from regular use of Wobenzym®. The first would be the ability of Wobenzym® N to improve athletic performance by decreasing the inflammatory consequences of that intense physical activity brings about. While the demands of athletic performance tend to improve physical health and cumulatively improve further athletic performance, over training and excessive strain leads to tissue damage with the undesirable consequence of inflammation.
Most of us have experienced the increased achiness that is common after exercise – sometimes it shows up a couple of days after the workout. This represents a degree of inflammation that the body has to recover from.
Think of this a micro-trauma. There is not a bruise, sprain or broken bone, but there is inflammation. Now, as far as the body is concerned, inflammation is inflammation – so the body's resources are being used to react to that inflammation. Specifically; cytokines – those inflammation promoting molecules we have talked about – are increased after intense physical exercise.
As we discussed earlier, Wobenzym® N decreases pro-inflammatory cytokines. As such, it shortens the duration of post exercise inflammation.
The excellent results have been observed in athletes using Wobenzym® N can be explained by its ability to interfere with the inflammation caused by athletic micro-trauma. In this fashion, it improves recovery time.

What about the times that there is a little more than "micro-trauma"- when sports activity actually results in a bruise, sprain or broken bone? Can Wobenzym® N improve recovery time in those situations?
Actually, that is one of the greatest benefits of using Wobenzym® N - its ability to dramatically improve recovery from trauma. Learn more in the section on sports medicine
What we see, and what the literature also discusses, is that Wobenzym® N shortens recovery from sport injuries, such a sprains and hematomas. Even in cases where a sports injury required surgery to repair a break, Wobenzym® N shortened recover time after surgery. This is beneficial to both the professional athlete, and to non-professionals – who want to get back in the game and spend less time recuperating on a couch.
Specifically, a double blind, placebo controlled randomized clinical trial showed that karate fighters taking 5 tablets or Wobenzym®, 3 times a day recovered four times as fast as other sportsmen will the same injuries. They concluded that top sportsmen who are at a higher risk of injury can resume training, and have less time away from work when they take Wobenzym® on a regular basis.
Weekend athletes should keep this research in mind.

What about those sever injuries that require surgery? Does Wobenzym® N make a difference in those situations?
Absolutely! The ability to shorten recovery time after surgery is very impressive. Research has showed that taking Wobenzym® for seven days before surgery cut the amount of pre-surgical swelling due to trauma in half – which is very important since you want as little swelling as possible before going into surgery. Patients who did not take Wobenzym® while waiting for the surgery had twice as a much swelling.
After surgery, the swelling in patients taking Wobenzym® was once again cut in half and allowed patients to get off of pain meds much quicker. They also noted a significant decrease in both CRP and ESR – which are typically elevated after trauma and surgery. Learn more at: Sports Medicine
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.
Wobenzym® N is also the best choice for treating the aches and pains that can occur after strenuous physical activity. It does not have the side effects of aspirin and other non-steroidal anti-inflammatory drugs. It is not as dangerous to the liver as acetaminophen. I also find that it dramatically reduces the aches and pains that can happen after working out at the gym.
Many serious athletes, including some who compete in iron-man competitions, consider Wobenzym® to be an important part of their athletic program. Athletic performance is a real quality of life and "wellness" issue for many people. So it's important to know that Wobenzym® N can also be used for general wellness as well as the different diseases that it is used for.

Using Wobenzym® For Treating Diseases of Brain & Nervous System

What do we know about the benefits of Wobenzym® on the nervous system?
The nervous system is just as sensitive to the assaults of systemic inflammation as other body systems. Inflammation plays a critical role in the development of debilitating neurological conditions such as Alzheimer's disease, which some doctors describe as "the brain on fire". In fact, it is now more appropriate to call Alzheimer's and inflammatory disease. The phrase "degenerative brain disease" does not appropriate describe the fact a root cause is the active inflammation taking place in the brain.
We now know that systemic inflammation increases production of the pro-inflammatory cytokine TNF-alpha (tumor necrosis factor alpha).
A recent study of three hundred patients noted that increased serum levels of TNF-alpha due to systemic inflammation are associated with increased rate of cognitive decline.
Research has shown, without a doubt, that Wobenzym® decreases serum levels of TNF-alpha. As we saw in the rheumatoid arthritis studies, patients treated with Wobenzym® have TNF-alpha levels less than half the levels seen in untreated patients. This decrease is the pro-inflammatory cytokine TNF-alpha is one of the mechanisms by which Wobenzym® can decrease the progression of Alzheimer's disease.
I cannot overemphasize how important it is to have TNF-alpha levels lowered. If the levels of that pro-inflammatory cytokine are not kept in check, we see increased production of amyloid beta peptides, the main component of the plaques that appear in the brains of Alzheimer's patients. By decreasing TNF-alpha, Wobenzym® can decrease the formation of those dangerous amyloid beta peptides.

Another important finding is that Wobenzym® can promote the breakdown and clearance of these amyloid beta peptides. A number of studies show that when alpha-2-macroglobulin is activated the amyloid beta peptides are one of the biomarkers of inflammation that are broken down, and removed from tissues at an accelerated rate.

Are there other diseases of the nervous system that Wobenzym® can help?
Multiple sclerosis patients treated with Wobenzym® showed a decreased number of attacks and a shortened duration of those fewer attacks that did occur. The studies conclude that the stabilization of the nervous system and the improved activities of daily living were a direct result of the decreased inflammatory activity due to use of Wobenzym®.
From what we know about diseases and dysfunctions of the nervous system, it would be fair to say that any nerve problem that is due to inflammation can be improved by Wobenzym®.

Even nerve conditions like sciatica?
There is a significant amount of research showing that lowering TNF-alpha levels is the key to treating sciatica. There is a focus on using pharmacological agents that are injected to decrease TNF-alpha. Unfortunately, those injections carry – what the manufacturer calls "serious (sometimes fatal) side effects". There is no doubt that decreasing TNF-alpha will fix sciatica. It is also obvious that Wobenzym® is a safe and effective way of accomplishing that goal.
Bells' palsy is also associated with increased pro-inflammatory cytokines, including high TNF-alpha. The high TNF-alpha in patients with Bell's palsy is considered a key factor in the development of the disease.

What about the numbness that can happen with diabetes?
TNF-alpha and interleukin-6 are both increased in patients with type 1 diabetes mellitus and diabetic neuropathy. Wobenzym® lowers these pro-inflammatory cytokines, so we again can see protection from diabetic neuropathy. When Wobenzym® was added to the therapies for children with type 1 diabetes, we see lower HbA1c, and higher levels of C-peptide. C-peptide, a marker of how much insulin the pancreas can still make, decreases the onset and progression of the complications of diabetes such as diabetic neuropathy.
In fact, C-peptide decreases the progression of many diabetes-related complications. By helping the body raise c-petide levels, Wobenzym® also decreases the risk and progression of diabetes kidney disease a very common complication that can occur with diabetes. That is just one the benefits that Wobenzym® has for diseases of the kidneys.

Kidney and Bladder Conditions & Wobenzym®

How can Wobenzym® decrease the risk of developing kidney stones?
In the most severe cases of kidney stones - patients that need surgical intervention to remove the stones – taking the systemic enzymes made them significantly less likely to get stones again.
Now what is interesting is that in those studies, the patients took enzymes for only four to five weeks – but they still had less risk of developing new kidney stones a year later!!
From what I have been able to find in the literature, I would say that by decreasing inflammation (and decreasing pro-inflammatory cytokines such as IL-6 – which is associated with kidney stone formation), and pro-Wobenzym® is able to inhibit the development of kidney stones decrease the inflammatory.
But more than that, the enzymes in Wobenzym® have proteolytic properties may decrease formation of the organic (protein) component of the kidney stone. In addition, the enzymes appear to be interacting with bikunin, a glycoprotein that is a member of the inter-alpha-trypsin inhibitor (ITI) family. Like alpha-2-macroglobulin, the ITI family of glycoproteins modulate inflammation. Proper function of bikunin decreases calcium oxylate stone formation.
We also note that patients with kidney stones complicated by pyelonephritis have very high levels of SIgA (secretory IgA) an immunoglobulin involved in local immunity of mucus membranes. This increase in the urine level of SIgA in patients with kidneys stones and pyelonephritis can play apart in the development of kidney stones. By normalizing urinary system local immunity, Wobenzym® can decreases kidney stone formation. So, there are a number of mechanisms by which Woebnzym-N can decrease kidney stone formation.

How are kidney infections improved by using Wobenzym®?
In a study of 66 patients with chronic pyelonephritis, Wobenzym® yielded results that "considerably exceeded those in conventional drug treatment." This was evidenced by both clinical findings (symptoms) as well as laboratory findings.
One reason for the notable benefit would be due to the normalization of urinary system local immunity, as we just discussed.

Now I will be the first to admit that kidney infections are serious conditions, and antibiotic therapy is very appropriate therapy. But what we have observed is that chronic and recurrent infections – infections that are resistant to improvement even on antibiotics – do much better – and can be resolved when Wobenzym® is added to the treatment plan. Other conditions that are often resistance to antibiotic therapy and benefit from this systemic enzyme therapy also include and recurrent urinary tract infections, a very common problem of the urinary system.

Is Wobenzym® useful for treating urinary tract infections?
Adding enzyme therapy to the antibiotic therapy dramatically shortens the time that it takes both feel better, and for lab tests to show a decrease in the systemic inflammation that accompanies a urinary tract infection. This has been observed in the recurrent urinary tract infections – which have traditionally been very hard to treat –even with antibiotics and other drugs.
Keep in mind, these recurrent urinary tract infections are notorious for being hard to treat and hard to keep coming back. The fact that we can use Wobenzym® to make antibiotics more effective – and to prevent re-infection – is a very important point.
When we use Wobenzym® to make antibiotic more effective we are using the adjuvant properties of Wobenzym®. An adjuvant is a substance that significantly improves the effective of other therapies that have limited effectiveness. Wobenzym® has been used as an adjuvant to treat a number of inflammatory and infectious diseases. This hold true for not only recurrent urinary tract infections and pyelonephritis, but also for recurrent respiratory tract infections, as well as chronic infections of the reproductive system.

How does Wobenzym® help glomerulonephritis?
The benefits of Wobenzym® in regards to the treatment of glomerulonephritis is due to many beneficial actions of Wobenzym® including among other actions, its antioxidant effect, its anti-inflammatory functions, and its ability to restore normal lipid (fats) metabolism. One study concludes that Wobenzym® is the drug of choice, decreasing the velocity of kidney destructive processes. Learn more in the section on glomerulonephritis.

How does Wobenzym® help with diabetic kidney disease?
We know that Wobenzym® can increase levels of C-peptide in autoimmune mediated diabetes, such as type 1 diabetes. In addition to showing much insulin the pancreas can still make, C-peptide decreases the progression so the common complications of diabetes, including the diabetic nephropathy.
We also note that systemic enzymes can decrease the formation of “advanced glycation end products” (AGEs), which are associated with diabetic nephropathy and other complications of diabetes.
In addition, abnormal cytokines levels are normalized, including transforming growth factor beta-1 (TGF-b1), and interleukin 6.
What we have come to realize, is that the complications of diabetes are strongly mediated by the immune system. We see that controlling blood sugar with insulin is not enough to prevent complications such as diabetic nephropathy. The abnormal cytokine levels that occur with diabetes can safely and effectively be normalized with Wobenzym®.
This normalization of immune function is why Wobenzym® should also be used in other kidney diseases such as kidney stones, frequent urinary tract infections and pyelonephritis.

Respiratory Conditions & Wobenzym®

How does Wobenzym® N can help patients with chronic recurrent respiratory infections?
In two separate studies, we have seen that Wobenzym® dramatically reduces the sickness rate in children that have frequent respiratory tract infections. The sickness rate in Wobenzym-treated children was reduced by 65.2 % and reduction of antibiotic consumption was 71.8 %. The decreased need for antibiotics is of course impressive. On average, the children were sick over 5 times a year before taking Wobenzym®. Atfer taking Wobenzym® they got sick less than twice a year. The Wobenzym-treated children also benefited from not having elevated temperature and feeling less tired.
We should keep in mind, that in these cases the children were traditionally treated with antibiotics, but the course of the infection took long to resolve, and the patients had recurrent infections – they were in and out of the hospital over 5 times a year.

Wobenzym® is used as an adjuvant in these cases to make antibiotics more effective - but more importantly to improve immune function so that the patients did not keep getting sick. So Wobenzym® acted as both an adjuvant and as an immunomodulator – restoring balance to the immune system.

What are some other specific respiratory infections that benefit Wobenzym® N?
Specific respiratory tract infections include bronchitis, laryngitis, tonsillitis, and even pneumonia. In fact, when Wobenzym® was added to the traditional antibiotic therapy there was a notable acceleration of healing time, which was evidenced in both the x-rays and lab tests, as well as the patients' clinical symptoms.

What about allergic symptoms?
In one of the mentioned studies, a Wobenzym® treatment caused a reduction of allergic manifestations, such as nose obstruction and burning eyes during pollen season - which persisted even under treatment with antihistamines - was observed in children with proven pollen allergies.
Another study of patients with asthma had significantly reduced frequency of acute diseases and were often able to reduce their dosage of inhalation corticoids.
We should also note that eczema is also improved with Wobenzym®.
As you know, asthma, eczema and allergies (eyes & nose) make up the "allergic triad".

Could Wobenzym® N help with seasonal allergies?
Noting that Wobenzym® is effective in treating each of these difficult conditions, we can say without a doubt that people with allergies – including seasonal allergies – would benefit greatly by taking Wobenzym® N.

What about chronic sinusitis?
I have seen good results when using Wobenzym® to treat chronic sinusitis. Which of course makes sense. Chronic recurrent sinusitis is typically a condition that has both allergic and infectious components – due to unstable local immunity. Wobenzym® N is able to balance the immune system and decrease the occurrence of sinusitis and help is resolve much quicker.

Eyes, Ears, Nose & Throat Conditions & Wobenzym®

How effective is Wobenzym® for the treatment of eye conditions such as uveitis?
When treated with the Wobenzym® PS formulation, 60% of patients with anterior uveitis were improved within about 17 days. I believe this data can be used to treat posterior uveitis based on the ability of Wobenzym® to decrease TNF-alpha levels (a pro-inflammatory cytokine), and the current trend to use anti-TNF alpha antibodies to treat posterior uveitis.

What about conditions which cause uveitis, such as Behçets Disease?
Patients with Behçets Disease who did not have adequate therapeutic results from conventional therapy were started on Wobenzym® therapy, which resulted in positive results in 90% of treated patients.

Does Wobenzym® help with chronic middle ear inflammation?
The formulation as an adjuvant significantly improved clinical outcomes in 60% of children suffering from chronic secretory otitis and had a positive influence on speech therapy in 83% of children.

Skin Conditions & Wobenzym®

How is Wobenzym® used in the treatment of eczema?
Wobenzym® has been shown to be effective in the treatment of eczema when used alone or in combination with other therapies. The research shows that some patients have a slight increase in itching for the first 4-5 days - possibly due to the speeding up and modulation of inflammatory processes and because of local microcirculation improvement. However, in the following days the intensity of itching became rapidly decrease, so that by 15 to 18 days the intensity of skin itching became insignificant or disappeared all together, and improved skin health with decreased rash.

I should point out that eczema is often resistant to conventional therapies, and even dietary modification does not fix most cases. I suspect this is because the body is stuck in a chronic cycle of inflammation. This is why the immunomodulatory effects of Wobenzym® N are so important.
In the most resistant cases, 3 months of Wobenzym® N added to a good dietary regiment can bring improvement by arresting the inflammatory cycle. Once arrested, the improvement will continue even after discontinuation of therapy.

What about psoriasis?
Psoriasis is another one of those conditions that require dietary changes as well. But even then, it is difficult to get rid of because – again - because the body is stuck in a chronic cycle of inflammation.
Psoriasis is another one of those conditions that have high amount of the pro-inflammatory cytokine TNF-alpha (tumor necrosis factor alpha). It is known that TNF alpha is elevated in both the skin patients with psoriasis. We also know that Wobenzym® decreases TNF-alpha levels.
So, it should come as no surprise, when we learn that when Wobenzym® is used, there is a marked improvement of clinical symptoms and as well as laboratory values in patients with psoriasis.

What about scars on the skin, does Wobenzym® N help with that?
I note that surgical patients who take Wobenzym® do not develop those large keloid scars seen in other patients. I have also seen that patients not only had almost unperceivable surgical scars when they use Wobenzym® N with for surgeries, but I have seen older scars become significantly reduced – to the point that they were almost invisible. I have heard this from other practitioners as well.
Knowing what we do about the immunomodulation properties of Wobenzym® we should not be surprised to see it decreases scar tissue formation.
Excessive scarring is due to an altered production of cytokines, specifically – TNF-alpha. Just as Wobenzym® N decreases TNF-alpha levels in the skin of patients with psoriasis, it can also decrease the levels of TNF-alpha in scar tissues. As a result, we see reduced postsurgical scarring, and reduction of older scars.

What about acne scars?
I would say that acne scars can definitely be reduced by taking Wobenzym® N. I have seen acne scars that are years old disappear after a patient was taking Wobenzym® N for a joint injury. I think it is safe to say that Wobenzym® N should b considered for any disorders of the skin.

Hormones & Wobenzym®

How can Wobenzym® be used for the treatment of hormone imbalances?
Wobenzym® is the answer to a to a very effectively in controlling the inflammation that is related to hormone imbalances. What we now understand, is that elevated levels of pro-inflammatory cytokines in various endocrine problems– such as interleukin 6 and TNF-alpha are restored to normal with the various Wobenzym® formulations.

Elevations of those proinflammatory cytokines are now recognized in menopause, hypothyroidism, polycystic ovary disease, insulin resistance, diabetes, infertility and even adrenal fatigue and stress disorders.
We also know that elevated pro-inflammatory cytokines interfere with normal function of the hypothalamic-pituitary axes.
Specifically, these cytokines inhibit the activity of the hypothalamic-pituitary-adrenal axis – causing abnormal circadian (24 hour) rhythms, and predisposing to, or perpetuating fatigue disorders.
We know that inflammatory cytokines inhibit the activity of the hypothalamic-pituitary gonadal (HPG) axis at various levels and that this dysregulation of the gonadal axis may chronically lead to reproductive dysfunction and reduced fertility. [PMID19121989] We also know that inflammation can have a direct affect on the function of ovaries and testes and negatively affect fertility.
Thyroid function can likewise be negatively affected. Elevations of pro-inflammatory cytokines interfere with normal hypothalamic-pituitary-thyroid axis function. In addition, the cells within the thyroid – the thyrocytes have diminished ability to function due to this systemic inflammation. In fact, controlling systemic inflammation may be the most important therapy in overcoming subclinical hypothyroidism. There is already no doubt in my mind that Wobenzym® should always be considered for autoimmune thyroid disease.

What role does Wobenzym® play in the treatment of thyroid disease?
Autoimmune hypothyroidism (Hashimoto's) – the most common cause of hypothyroidism - is a condition that can be somewhat difficult to successfully treat due to the chronic inflammation taking place in that condition. Even after the patient's hormone levels have been increased back to normal with prescription thyroid replacement, we still see many clinical signs of hypothyroidism.
For instance, even after thyroid hormone replacement, patients can still have elevated cholesterol and triglycerides. However, when patients were given 5 Wobenzym® tablets, 3 times a day – in addition to their thyroid replacement – their cholesterol and triglycerides decreased. The patients that were only given thyroid replacement still had elevated cholesterol and triglycerides.
We also noted that taking Wobenzym® resulted in a reduction of autoimmune antibodies that attack the thyroid – the anti-TG and anti-TPO antibodies. Since the thyroid is no longer under attack from the immune system, it is able to resume making thyroid hormones that way that it should. As a result, there was also a reduction of TSH levels. As a result, patients that received Wobenzym® as part of their therapy were able to lower their dosage of thyroid medication after 3 months. In some cases, the thyroid medication could be completely discontinued.
Based on what we now know, I would say that this is possible because of Wobenzym's beneficial effect on the hypothalamic-pituitary-thyroid axis, - its effect on the thyroid tissue itself – and its effect on the immune system - the elimination of autoimmune destruction of the thyroid.
The pro-inflammatory cytokines that we see in both autoimmune disease and in systemic inflammation have a very detrimental effect on thyroid function on so many levels. If we keep in mind that the first word in the phrase "autoimmune thyroid disease" is "autoimmune" we will have a better understanding of why the immunomodulating properties of Wobenzym® N are so effective in treating autoimmune hypothyroidism.

What affect does Wobenzym® therapy have on the development and progression of diabetes?
When Wobenzym® was added to the therapies for children with type 1 diabetes, we see lower HbA1c, and higher levels of C-peptide. When there is an increase in C-peptide, a marker of how much insulin the pancreas can still make, there is decreases the onset and progression of the complications of diabetes such as diabetic neuropathy. By helping the body raise c-petide levels, Wobenzym® also decreases the risk and progression of diabetes kidney disease a very common complication that can occur with diabetes. That is just one the benefits that Wobenzym® has for diseases of the kidneys.
Animal studies on development of diabetes demonstrate that Wobenzym® PS decreases the development of antibodies against pancreatic islet cells.

How does Wobenzym® help with diabetic kidney disease?
We know that Wobenzym® can increase levels of C-peptide in autoimmune mediated diabetes, such as type 1 diabetes. In addition to showing much insulin the pancreas can still make, C-peptide decreases the progression so the common complications of diabetes, including the diabetic nephropathy.
We also note that systemic enzymes can decrease the formation of "advanced glycation end products" (AGEs), which are associated with diabetic nephropathy and other complications of diabetes.
In addition, abnormal cytokines levels are normalized, including transforming growth factor beta-1 (TGF-b1), and interleukin 6.
What we have come to realize, is that the complications of diabetes are strongly mediated by the immune system. We see that controlling blood sugar with insulin is not enough to prevent complications such as diabetic nephropathy. The abnormal cytokine levels that occur with diabetes can safely and effectively be normalized with Wobenzym®.
This normalization of immune function is why Wobenzym® should also be used in other kidney diseases such as kidney stones, frequent urinary tract infections and pyelonephritis.

Why has Wobenzym® been used for infertility?
Wobenzym® N has been used in the treatment of infertility for a number of reasons. First, elevated cytokines – which are frequently seen in infertility - interfere with normal function of the hypothalamic-pituitary axes. This results in altered production of pituitary hormones that are critical for fertility. So, the one benefit of Wobenzym® N is the normalization of the hypothalamic-pituitary-gonadal axis.
Another benefit would be an improvement of immunologically caused habitual miscarriages, which can be because of either autoimmune or alloimmune dysfunction. In autoimmune infertility, the miscarriage is because of autoimmune

inflammation that prevents proper function of the placenta due to inflammation. In alloimmune miscarriages, the mother's immune system is so unstable due to abnormal inflammatory action that it actually attacks the fetus and causes the miscarriage.
The literature reveals that Wobenzym® is an effective therapy for autoimmune and alloimmune miscarriages. One study showed that 124 out of 144 women who had habitual immunologically caused miscarriages were able to get pregnant and give birth to 114 healthy children. Those are pretty impressive results.

How else can Wobenzym® be used in women's health?
Quite a few conditions are improved by adding Wobenzym® to the treatment plan. We see it used with various forms of both acute and chronic pelvic inflammatory disease.
Wobenzym® is very effective therapy for the management of fibrocystic breast disease, especially since it does not interfere with already upset hormonal balance that typically accompanies fibrocystic breast disease.

What about men? Does it help with prostate problems?
In men, Wobenzym® is a very efficient therapy for both bacterial and abacterial prostatitis, and also relieves the sexual dysfunction that typically accompanies prostate diseases.

Dosages, Contraindications & Cautions & More Information

Please see the section on Dosage Guidelines, which is before the FAQ section of this book.

What is the common dosage for Wobenzym®, and can the dosage be different for some people?
An effective dosage of three tablets of Wobenzym® N two times a day is referenced in the literature. Higher dosages may be used if clinically indicated. The preponderance of clinical studies has shown the formulation to be very effective at a dosage of 5 tablets 3 times a day, 7 tablets 3 times a day, and 10 tablets 3 times a day. The tablets should always be taken at least 45 minutes before a meal, with a large glass of water. Children's dosage is based on weight in kg, and is discussed in detail in the Dosage Guidelines section, which is before the FAQ section of this book.

Can someone take too much Wobenzym®?
The most common observed side effect with very high dosages is occasional gastrointestinal symptoms such as increased number of softer bowel movements, but this effect disappears as soon as the dosage is reduced, or it will typically decrease in a couple of weeks if the patients wants to stay on the higher dosage because of the great therapeutic effects. As always, it is important to work with your personal physician whenever you take any supplement in dosages that are higher than the dosage listed on the label of the supplement.

How long should someone take Wobenzym®?
The literature has a number of reports of the best treatment time at which clinical improvement is observed, and I would have to say I agree with what I have read, based on my experiences with Wobenzym®.
Chronic illnesses, especially those with an autoimmune or immune senescence component, benefit from long term therapy to maintain effective immunomodulation. That may be 1 to 2 months for chronic conditions like gout, eczema or lyphedmema. In aggressive autoimmune diseases like rheumatoid arthritis, patients benefit from staying on Wobenzym®, and remain on it for years.
The length of treatment is typically 2 -6 weeks for acute conditions.

What about side effects?
An excessive dose may lead to adverse effects in the form of increased softer bowel movements, but this effect disappears as soon as the dosage is reduced, or typically decrease in a couple of weeks if the patients wants to stay on the higher dosage because of the great therapeutic effects.
Occasionally, temporary aggravation of symptoms may occur at the beginning of treatment in chronic diseases. Based on current experience and review of the literature, such a transient aggravation is regarded as a positive reaction of the body

to the therapy in most cases. In such an event, administration of the drug should not be discontinued but a possible temporary reduction in dosage should be considered.

Is there a chance of allergy to systemic enzyme formulations?
People with known allergies to any specific ingredient in any product should of course avoid the product. If there is a know allergy to papaya, consider a formulation without papaya. It should be noted that there may be some cross reactivity between papaya, avocados, potatoes, bananas, tomatoes, chestnuts and kiwi fruit allergies as well as latex allergies, so an allergy to any of these foods or substances may indicate an allergy to the other foods or substances. Individuals with allergies should always seek the approval of their healthcare professional before starting any supplement program.

How long can systemic enzyme therapy drugs be taken for?
No adverse effects (except looser stools) have been observed even when higher doses of enzyme preparations were administered for a long time.

How are systemic enzyme therapy drugs administered?
The tablets need to be swallowed, without chewing, on an empty stomach, i.e. at least 45 minutes before the next meal or at least 2 hours after the last meal and rinsed down with plenty of liquid (at least 250 ml).

May systemic enzyme therapy be used by children?
The enzyme preparations may be given to children after a consultation with a physician who will prescribe the dosage. The literature reveals children respond very well. Children's dosage is based on weight in kg, and is discussed in detail in the Dosage Guidelines section, which is before the FAQ section of this book.

If someone has more questions, or wants more information, where can they get it?
They should first talk to their physician, pharmacist or othere healthcare professional who is experienced in the use of Wobenzym® formulations.

Dosage Guidelines for the Wobenzym® Formulations

Based on a review of international literature by Joseph J Collins, RN, ND

Wobenzym® N

Label Dosage: 3 tablets, twice a day

International: Wobenzym® N is called Wobenzym® in Germany and other countries.

Effective Dosage
An effective dosage of 3 tablets 2 times a day is referenced in the literature. Higher dosages may be used if clinically indicated.

Other Dosages
Several clinical studies has shown the formulation to be very effective at a dosage of 5 tablets 3 times a day, 7 tablets 3 times a day, and 10 tablets 3 times a day. The tablets should always be taken at least 45 minutes before a meal, with a large glass of water. Children's dosage is based on weight in kg.

Duration: The literature reports treatment time at which clinical improvement is observed. Chronic illnesses, especially those with an autoimmune or immune senescence component, benefit from long term therapy to maintain effective immunomodulation. Supplementation is predominantly 2 -6 weeks for acute conditions. Duration of supplementation for chronic conditions may be from 1 – 2 months, or years as indicated.

Clinical Application: The following table includes references pertaining to conditions treated with the Wobenzym® N formulation. The clinical efficacy in treating inflammatory, autoimmune, traumatic, and infectious conditions supports its additional use in a wide range of other clinical conditions.

Comparing Wobenzym® N to Wobenzym® PS dosages, and Wobenzym® Plus dosages
In adults, 30 Wobenzym® N tablets (10 tablets, three times a day) may be substituted with 6 Wobenzym® PS tablets (2 tablets, three times a day) [28].

Children Dosages
In children, Wobenzym® N tablets at 1 tablet per6 (six) kg body weight may be substituted with Wobenzym® PS tablets at 1 tablet / 10 kg body weight up to maximum six tablets a day. As such, the daily dosage for a 30 kg child would be 5 Wobenzym® N tablets or 3 Wobenzym® PS tablets [29] [30].
Two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets. Therefore, in the above example, the daily dosage for a 30 kg child would be two Wobenzym® Plus tablets.

Crushed Tablet Dosing
If unable to swallow the whole tablet, may use crushed tablets strictly on empty stomach with plenty of water and increase the dosage by another 50%. As such, a dosage of 2 tablets t.i.d. would be increased to 3 crushed tablets t.i.d. on empty stomach with plenty of water. [31], [32]

References: See References Section at end of book.

Wobenzym® PS

Label Dosage: 3 tablets, twice a day

International: Wobenzym® PS is known as Phlogenzym in Germany and other countries.

Effective Dosage
The preponderance of clinical studies has shown the formulation to be very effective at a dosage of 6 tablets per day, taken as either 3 tablets twice a day, or 2 tablets three times a day at least 45 minutes before a meal, with a large glass of water.

Other Dosages
Higher dosages may be used if clinically indicated (see table). Children's dosage is based on weight in kg.

Duration
Literature reports treatment time at which clinical improvement is observed. Supplementation is predominantly 3 weeks for acute conditions. Duration of supplementation for chronic conditions may be from 1 month to 3 months, or years as indicated.

Clinical Application
The following table has a sample of conditions treated with the Wobenzym® PS formulation. The clinical efficacy in treating inflammatory, autoimmune, traumatic, and infectious conditions supports its additional use in a wide range of other clinical conditions.

Comparing Wobenzym® PS to Wobenzym® N dosages
In adults, 6 Wobenzym® PS tablets (3 tablets, two times a day) may be substituted with 30 Wobenzym® N tablets (10 tablets three times a day) [56]. In children, Wobenzym® PS tablets at 1 tablet / 10 kg body weight up to maximum six tablets a day may be substituted with Wobenzym® N tablets at 1 tablet / 6 kg body weight. As such, the daily dosage for a 30 kg child would be 3 Wobenzym® PS tablets or 5 Wobenzym® N tablets. [57], [58]

Comparing Wobenzym® N to Wobenzym® PS dosages, and Wobenzym® Plus dosages
In adults, 30 Wobenzym® N tablets (10 tablets t.i.d.) may be substituted with 6 Wobenzym® PS tablets (2 tablets, t.i.d.) [60].

Children Dosages
In children, Wobenzym® N tablets at 1 tablet / 6 kg body weight may be substituted with Wobenzym® PS tablets at 1 tablet / 10 kg body weight up to maximum six tablets a day. As such, the daily dosage for a 30 kg child would be 5 Wobenzym® N tablets or 3 Wobenzym® PS tablets. [57], [58]
Two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets. Therefore, in the above example, the daily dosage for a 30 kg child would be two Wobenzym® Plus tablets.

Crushed Tablet Dosing.
If unable to swallow the whole tablet, may use crushed tablets strictly on empty stomach with plenty of water and increase the dosage by another 50%. As such, a dosage of 2 tablets t.i.d. would be increased to 3 crushed tablets t.i.d. on empty stomach with plenty of water. [59], [60]

References: See References Section at end of book.

Wobenzym® Plus

Label Dosage: 2 tablets, twice a day

International: This Dosage Guideline summary for Wobenzym® Plus is based on a review of international literature by Joseph J Collins, RN, ND on the published dosages for Wobenzym® PS. Wobenzym® PS is known as Phlogenzym in Germany and other countries.
Note: Two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets.

Effective Dosage: Based on the conversion of three (3) Wobenzym® PS tablets to two (2) Wobenzym® Plus tablets, the preponderance of clinical studies has shown the formulation to be very effective at a dosage equal to four (4) Wobenzym® Plus tablets per day, often taken as **two (2) Wobenzym® Plus tablets twice a day, at least 45 minutes before a meal**, with a large glass of water. Higher dosages may be used if clinically indicated. Children's dosage is based on weight in kg.

Duration: Literature reports treatment time at which clinical improvement is observed. Supplementation is predominantly 3 weeks for acute conditions. Duration of supplementation for chronic conditions may be from 1 month to 3 months, or years as indicated.

Clinical Application: The following table has a sample of conditions treated with the formulation. The clinical efficacy in treating inflammatory, autoimmune, traumatic, and infectious conditions supports its additional use in a wide range of other clinical conditions.

Comparing Wobenzym® PS to Wobenzym® N dosages
In adults, 6 Wobenzym® PS tablets (3 tablets, two times a day) may be substituted with 30 Wobenzym® N tablets (10 tablets three times a day) [56].

Comparing Wobenzym® N to Wobenzym® PS dosages, and Wobenzym® Plus dosages
In adults, 30 Wobenzym® N tablets (10 tablets t.i.d.) may be substituted with 6 Wobenzym® PS tablets (2 tablets, t.i.d.) [60].

Children Dosages
In children, Wobenzym® N tablets at 1 tablet / 6 kg body weight may be substituted with Wobenzym® PS tablets at 1 tablet / 10 kg body weight up to maximum six tablets a day. As such, the daily dosage for a 30 kg child would be 5 Wobenzym® N tablets or 3 Wobenzym® PS tablets. [57], [58]
Two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets. Therefore, in the above example, the daily dosage for a 30 kg child would be two Wobenzym® Plus tablets.

Crushed Tablet Dosing.
If unable to swallow the whole tablet, may use crushed tablets strictly on empty stomach with plenty of water and increase the dosage by another 50%. As such, a dosage of 2 tablets t.i.d. would be increased to 3 crushed tablets t.i.d. on empty stomach with plenty of water. [59], [60]

References: See References for Wobenzym® PS at end of book, noting that the dosages of Wobenzym® Plus have been reduced to reflect that two (2) Wobenzym® Plus tablets are equal to three (3) Wobenzym® PS tablets

Formulation:	Wobenzym® N	Wobenzym® PS	Wobenzym® Plus
Label Dosage	**3 tablets BID**	**3 tablets BID**	**2 tablets BID**
Dosage Equivalence	**5 tablets**	**3 tablets**	**2 tablets**
Ankle Joint Distortion	≅ 10 tablets a day for 10 days	**6 tablets a day for 10 days [33], [34]**	≅ 4 tablets a day for 10 days
Arthritis; knee	≅ 10 tablets a day for 3 weeks	**6 tablets a day for 3 weeks [35], [36], [37]**	≅ 4tablets a day for 3 weeks
Arthritis; shoulder	≅ 10 tablets a day for 3 weeks to 7 weeks	**6 tablets a day for 3 weeks to 7 weeks [38]**	≅ 4 tablets a day for 3 weeks to 7 weeks
Bechet's disease	**7 tablets 3 times a day for ½ to 1 month (21 tablets a day) [1]**	≅ 4 tablets 3 times a day for ½ to 1 month	≅ 2 4 tablets 3 times a day for ½ to 1 month
Chronic Hepatitis B.	**7 tablets 3 times a day for 4 weeks followed by 3-4 tablets three times a day for 20 days as an adjuvant [2]**	≅ 4 tablets 3 times a day for 4 weeks followed by 2-3 tablets three times a day for 20 days as an adjuvant.	≅ 4 tablets 3 times a day for 4 weeks followed by 1-2 tablets three times a day for 20 days as an adjuvant.
Eczema (atopic dermatitis)	**2 tablets 3 times a day for 2 days, then 5 tablets 3 times a day for 1 ½ to 2 months, then 2 tablets 3 times a day long term to decrease risk of relapse, used as an adjuvant. [3]**	≅ 1 tablet 3 times a day for 2 days, then 3 tablets 3 times a day for 1 ½ to 2 months, then 1 tablet 3 times a day long term to decrease risk of relapse, used as an adjuvant.	≅ 1 tablet 3 times a day for 2 days, then 2 tablets 3 times a day for 1 ½ to 2 months, then 1 tablet 3 times a day long term to decrease risk of relapse, used as an adjuvant.
Fibromyalgia	≅ 10 tablets a day for 23 to 35 days.	**6 tablets a day for 23 to 35 days [39]**	≅ 4 tablets a day for 23 to 35 days
Gout	**5 tablets 3 times a day for 1 week, then 4 tablets 3 times a day for 7 days, then 3 tablets 3 times a day for 1 month as adjuvant [4]**	≅ 3 tablets 3 times a day for 1 week, then 2 tablets 3 times a day for 7 days, then 2 tablets 2 times a day for 1 month as adjuvant.	≅ 2 tablets 3 times a day for 1 week, then 2 tablets 3 times a day for 7 days, then 2 tablets 2 times a day for 1 month as adjuvant.
Hand surgery	**7-10 tablets 3 times a day, 7 days before surgery, followed by 12 days postoperatively. [5]**	≅ 4-6 tablets 3 times a day, 7 days before surgery, followed by 12 days postoperatively.	≅ 3-4 tablets 3 times a day, 7 days before surgery, followed by 12 days postoperatively.
Hematoma	≅ 10 tablets a day for 90 days.	**6 tablets a day for 90 days [40]**	≅ 4 tablets a day for 90 days.
Infertility & Chronic Salpingitis	**5 tablets 3 times a day for 10 or more days. [6] [7]**	≅ 3 tablets 3 times a day for 10 or more days.	≅ 2 tablets 3 times a day for 10 or more days.

References fro Dosage Guideklines: See References Section at end of book.

Formulation:	Wobenzym® N	Wobenzym® PS	Wobenzym® Plus
Label Dosage	**3 tablets BID**	**3 tablets BID**	**2 tablets BID**
Dosage Equivalence	**5 tablets**	**3 tablets**	**2 tablets**
Lymphedema	**9 tablets a day for 6 weeks [8], or 5 tablets 3 times a day for 6.5 weeks [9], or 3 tablets 3 times a day for 6 weeks as an adjuvant [10],[11]**	≅ 5 tablets a day for 6 weeks, or 3 tablets 3 times a day for 6.5 weeks, or 2 tablets 3 times a day for 6 weeks as an adjuvant.	≅ 4 tablets a day for 6 weeks, or 2 tablets 3 times a day for 6.5 weeks, or 1 tablets 3 times a day for 6 weeks as an adjuvant.
Multiple Sclerosis	**30 tablets a day as an adjuvant for 19 months [12]** (In divided dosages, such as 10 tablets, three times a day.)	≅ 18 tablets a day as an adjuvant for 19 months. (In divided dosages, such as 6 tablets, three times a day.)	≅ 12 tablets a day as an adjuvant for 19 months. (In divided dosages, such as 4 tablets, three times a day.)
Multiple Sclerosis	≅ 10ablets a day for 2 years.	**6 tablets a day for 2 years [41]**	≅ 4 tablets a day for 2 years.
Myocardial Infarction, post MI	**9 tablets for 30 days, as post MI adjuvant [13]**	≅ 5-6 tablets for 30 days, as post MI adjuvant.	≅ 3-4 tablets for 30 days, as post MI adjuvant.
Nephropathy, diabetic	≅ 10 tablets a day for 16 weeks.	**6 tablets a day for 16 weeks [42]**	≅ 4 tablets a day for 16 weeks.
Pelvic Inflammatory Disease, chronic	**5 tablets 3 times a day for 3 weeks [14]**	≅ 3 tablets 3 times a day for 3 weeks.	≅ 2 tablets 3 times a day for 3 weeks.
Postphlebitic syndrome	≅ 10 tablets a day for 3 months.	**6 tablets a day for 3 months [43]**	≅ 4 tablets a day for 3 months.
Prostatitis, chronic	≅ 10 tablets a day for 4 weeks.	**6 tablets a day for 4 weeks [44], [45]**	≅ 10 tablets a day for 4 weeks.
Psoriasis	**3 tablets 3 times a day (adjuvant) for 30 days [15]**	≅ 2 tablets 3 times a day (adjuvant) for 30 days.	≅ 1-2 tablets 3 times a day (adjuvant) for 30 days.
Radiomucositis; cancer	≅ 10 6 tablets a day for 10 days.	**6 tablets a day for 10 days [46]**	≅ 4 6 tablets a day for 10 days.
Respiratory Tract Infection, recurrent	**1 tablet per 6 kg body weight, divided into 2-3 sub-doses for 6 months in children 1 month to 15 years of age. [16]**	**1 tablet per 10 kg body weight, divided into 2-3 sub-doses for 6 months in children 1 month to 15 years of age. [47]**	≅ 1 tablet per 15 kg body weight, divided into 2-3 sub-doses for 6 months in children 1 month to 15 years of age.

References fro Dosage Guideklines: See References Section at end of book.

Formulation:	Wobenzym® N	Wobenzym® PS	Wobenzym® Plus
Label Dosage	**3 tablets BID**	**3 tablets BID**	**2 tablets BID**
Dosage Equivalence	**5 tablets**	**3 tablets**	**2 tablets**
Rheumatic Arthritis	**10 tablets 3 times a day for 15 days, then 7 tablets 3 times a day - 15 days, followed by 5 tablets 3 times a day - 30 days or longer [17], or 15-30 tablets a day for 6 months [18], or 15 tablets a day for 1 year [19], or 7-10 tablets 3x daily as an adjuvant for 2-4 weeks [20] [21] [22], or 30 tablets daily during the first month, then 15 tablets daily for a long-term treatment (years)[23]**	≅ 6 tablets 3 times a day for 15 days, then 4 tablets 3 times a day - 15 days, followed by 3 tablets 3 times a day - 30 days or longer, or 9-18 tablets a day for 6 months, or 9 tablets a day for 1 year, or 4-6 tablets 3x daily as an adjuvant for 2-4 weeks, or 18 tablets daily during the first month, then 9 tablets daily for a long-term treatment (years).	≅ 4 tablets 3 times a day for 15 days, then 3 tablets 3 times a day - 15 days, followed by 2 tablets 3 times a day - 30 days or longer, or 4-6 tablets a day for 6 months, or 6 tablets a day for 1 year, or 3-4 tablets 3x daily as an adjuvant for 2-4 weeks, or 12 tablets daily during the first month, then 6 tablets daily for a long-term treatment (years).
Rheumatoid Arthritis	≅ 10 tablets a day in the first 1½ to 2 months and then 21 tablets a day for 2 months to over 1 year. OR 10 tablets a day for 9 months. OR 10 tablets a day for 23 to 35 days.	**Wobenzym® PS at 6 tablets a day in the first 1½ to 2 months and then Wobenzym® N in the dosage of 21 tablets a day for 2 months to over 1 year [48].** **OR Wobenzym® PS at 6 tablets a day for 9 months [49].** **OR Wobenzym® PS at 6 tablets a day for 23 to 35 days [50]**	≅ 4 tablets a day in the first 1½ to 2 months and then 8 tablets a day for 2 months to over 1 year. OR 4 tablets a day for 9 months. OR 4 tablets a day for 23 to 35 days.
Sepsis in children	≅ 1 tablet per 6 kg body weight up to maximum six tablets a day in two or three divided doses for 14-21 days in children aged 1 month to 15 years.	**1 tablet per 10 kg body weight up to maximum six tablets a day in two or three divided doses for 14-21 days in children aged 1 month to 15 years. [51]**	≅ 1 tablet per 15 kg body weight up to maximum six tablets a day in two or three divided doses for 14-21 days in children aged 1 month to 15 years.
Sexual Dysfunction	**3 to 5 tablets three times a day for 2 -3 weeks [24]**	≅ 2 to 3 tablets three times a day for 2 -3 weeks.	≅ 1 to 2 tablets three times a day for 2 -3 weeks.
Sports Injury	**5 tablets 3 times a day prophylactically [25]**	≅ 3 tablets 3 times a day prophylactically.	≅ 3 tablets 3 times a day prophylactically.

References fro Dosage Guideklines: See References Section at end of book.

Formulation:	Wobenzym® N	Wobenzym® PS	Wobenzym® Plus
Label Dosage	**3 tablets BID**	**3 tablets BID**	**2 tablets BID**
Dosage Equivalence	**5 tablets**	**3 tablets**	**2 tablets**
Surgery	≅ 5 tablets, 3 times a day (9/day) for the first 3 days after surgery, then 3 tablets, three times a day.	**3 tablets, 3 times a day (9/day) for the first 3 days after surgery, then 2 tablets, three times a day [52]**	≅ 2 tablets, 3 times a day (9/day) for the first 3 days after surgery, then 1 tablet, three times a day.
Surgery	≅ 5 tablets 5 times a day for 2 to 6 days before surgery, then 5 tablets twice a day after surgery for 12 - 20 days.	**3 tablets 5 times a day for 2 to 6 days before surgery, then 3 tablets twice a day after surgery for 3-5 days, followed by Wobenzym® N , 5 tablets twice a day for 9 to 15 days. [53]**	≅ 2 tablets 5 times a day for 2 to 6 days before surgery, then 2 tablets twice a day after surgery for 12 - 20 days.
Tendonitis; shoulder	≅ 10 tablets a day for 3 weeks.	**6 tablets a day for 3 weeks [54]**	≅ 4 tablets a day for 3 weeks.
Thrombophlebitis	**10 tablets 3 times a day (30 tablets per day) for 15 days [26]**	≅ 6 tablets 3 times a day (18 tablets per day) for 15 days.	≅ 4 tablets 3 times a day (12 tablets per day) for 15 days.
Thyroiditis, Autoimmune	**5 tablets 3 times a day as an adjuvant for 6 months [27]**	≅ 3 tablets 3 times a day as an adjuvant for 6 months.	≅ 2 tablets 3 times a day as an adjuvant for 6 months.
Urinary tract infection; recurrent	≅ 10 tablets a day for 3 weeks.	**6 tablets a day for 3 weeks [55]**	≅ 4 tablets a day for 3 weeks.

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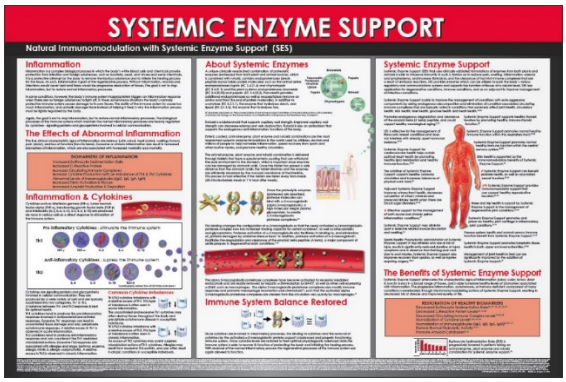

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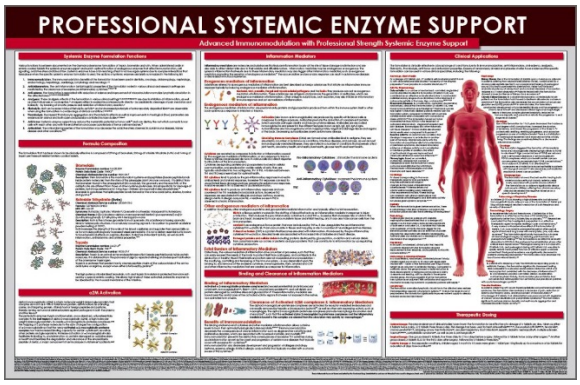

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Dosage Guidelines for the Wobenzym® Formulations

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