The Enzyme of Enzymes
by Dr. Nicholas Calvino

Recently a new metabolic, "biological" enzyme with potent fibrinolytic activity, that rivals pharmaceutical agents, has been discovered and shows great potential in providing support for hypercoagulative states and in supporting the activation of many of the body's 3,000 endogenous enzymes. This all-natural enzyme, Nattokinase (NK), is derived from a fermentation process of soy and the bacteria Bacillus natto. Already, backed by convincing and novel research, Nattokinase shows promise in supporting areas such as cardiovascular disease, stroke, angina, venous stasis, thrombosis, emboli, atherosclerosis, fibromyalgia/chronic fatigue, claudication, retinal pathology, hemorrhoid, varicos veins, soft tissue rheumatisms, muscle spasm, poor healing, chronic inflammation and pain, peripheral vascular disease, hypertension, tissue oxygen deprivation, infertility, and other gynecology conditions (e.g. endometriosis, uterine fibroids). To comprehend the magnitude of this new finding, a review of biological enzymes is necessary.

Enzymes, the Fountain of Life

Biological enzymes are enzymes which regulate endogenous chemical processes and have been called "the fountain of life" because without them, life could not exist. These enzymes speed and regulate all chemical reactions in the body in an orchestration of intelligence and control. Enzymes are made in the body from proteins and are provided by the ingestion of enzyme rich foods. During times of stress, sickness or reduced nutrient intake, the body can fall behind in the demand for the constant upkeep and creation of enzymes. Luckily the body has evolved to derive many of its enzymes from food, which helps to reduce the burden of the high enzyme production needs. Unfortunately, however, the enzyme content of foods has significantly decreased over the years due to processing, soil depletion, refining and preservation techniques of the food industry and a decreased consumption of fermented foods and fresh foods, which are high in enzyme content. Enzymes are an essential component of the diet - like vitamins, minerals, phytonutrients, fat, protein, carbohydrates, etc. - and without them, a deficiency state does occur. This deficiency state has been linked by various researchers, such as Dr. Edward Howell, Dr. M. Wolf, Dr. Francis Pottenger, Dr. Royal Lee, and Dr. Weston Price, to chronic disease, accelerated aging and premature death. Enzymes function by activating vitamins and minerals to forms usable by the body, by assisting in the liberation of nutrients from food, by helping to destroy harmful microbial agents, by signaling and regulating chemical processes (such as detoxification), and by activating other enzymes and hormones (cleaving zymogens → enzymes and pro-hormones → hormones).

There are three major groups of biological enzymes: (1) Food Enzymes, (2) Digestive Enzymes and (3) Metabolic Enzymes. In the past, the therapeutic use of enzymes has largely focused on the use of digestive enzymes. Digestive enzymes can be directly beneficial because they assist in digestion, help regulate immune responses in the intestinal tract, and relieve the body of its relative requirement of digestive enzyme production, allowing for biological energy and resources to be further allocated to the production of metabolic enzymes, indirectly.

Until now, the nutritional use of enzyme supplements has been almost exclusively in the form of Digestive Enzymes. Recently, however, a new Metabolic Enzyme has been isolated from a traditional fermented Japanese food (although it is consumed by other cultures in the same or similar forms), Natto, that appears to have metabolic effects and to work directly in concert with the metabolic enzymes. The name of this new enzyme is Nattokinase (meaning the enzyme from Natto) and has been called, "The Enzyme of Enzymes" by its discoverer, Dr. Hiroyuki Sumi. Natto has been used in Japanese culture for over 1000 years for its popular taste and as a folk remedy for heart and vascular diseases. Natto is produced by a fermentation process by adding Bacillus natto, a beneficial bacterium, to boiled soybeans. The resulting nattokinase enzyme is produced when Bacillus natto acts on the soybeans. Nattokinase has been the subject of 17 studies, including two small human trials. Nattokinase's most intriguing role promises to be its involvement in coagulation homeostasis. While other soy foods contain beneficial enzymes, it is only the natto preparation that contains the specific nattokinase enzyme.

Coagulation Homeostasis Overview

To understand the impact of Nattokinase on coagulation, a review of coagulation homeostasis and therapy is warranted. Some of the endogenous and exogenous agents involved in coagulation homeostasis are Plasmin, Heparin, Coumarin/Warfarin, and T-PA. However, most of these agents either have limitations, and/or serious side effects. A brief discussion on each:

- **Plasmin** is an endogenous protease that resembles trypsin (a digestive protease), and is the activated form of plasminogen. It is able to digest fibrin fibers, however, its limitation is that it is slowly activated, and therefore, slow acting, and works better to dissolve small clots, rather than larger ones.

- **Heparin** is a drug given IV that acts as an anticoagulant by inhibiting thrombin. Heparin is often associated with side effects, such as increased bleeding and hemorrhage.

- **Coumarin/Warfarin** is a drug that works by competing with vitamin K for reactive sites in the enzymatic process for the formation of prothrombin and clotting factors, thereby blocking the clotting action of vitamin K.

- **T-PA (Tissue Plasminogen Activator)** is a "clot buster" that is effective in activating plasminogen to plasmin. Although given as an IV drug, this is also a naturally occurring
substance produced endogenously, albeit in much smaller amounts.

- **Streptokinase** is another enzyme, derived from beta-hemolytic streptococci, which is used as a "clot buster." Its limitation is that its effect is rather short lived and eventually its therapeutic efficiency declines.

In addition to serious side effects and limitations, the "clot busters" lack true broad utility in that to be therapeutic, they must be injected. Therefore, there has been a renewed interest in discovering and using oral anti-clotting enzymes.

Fibrinolytic therapy by oral administration of enzymes was investigated by Sumi and co-workers over 10 years ago in an animal model where enteric-coated urokinase (UK) capsules were given to normal and experimental dogs with saphenous vein thrombosis. Previous findings indicated that intravenous (IV) administration did not show any clear thrombolytic effect, but that oral administration enhanced the fibrinolytic activity, serving as a treatment to lyse the thrombi in a mild but maintained way. The underlying mechanism of such fibrinolytic therapy by oral administration was then confirmed by basic research to involve absorption of the administered UK across the intestinal tract, and release into the blood of endogenous plasminogen activator which originated from the liver and/or endothelial cells. The enteric-coated UK capsules (60,000 U/day for 7 days) also exhibited a clinical efficacy against cerebral thrombi. Moreover, more effective results were obtained in double-blind tests at multicenter trials employing a dose of 120,000 U/day for 7 days. This supported the idea that oral enzyme agents can and do have systemic fibrinolytic properties, however, an oral fibrinolytic agent that had sustained activity and minimal side-effects was further pursued.

Nattokinase was later discovered by Dr. Sumi and research has found it to be a most promising agent as an ideal oral fibrinolytic agent—not only reversing clots but in preventing them and modulating the clotting process in ways that help re-establish coagulation homeostasis. Nattokinase is a serine endopeptidase with a molecular weight of 20,000 Daltons and a point of ionization (pI) of 8.6. This isolated fibrinolytic enzyme, derived from a traditional Japanese food, Natto, was discovered by Dr. Hiroyuki Sumi and resembles plasmin. Nattokinase is derived from the vegetable cheese, Natto, a typical and popular fermented soybean food in Japan. It shows potent fibrinolytic activity and was named Nattokinase (NK)—literally meaning, an enzyme derived from Natto. Dr. Hiroyuki Sumi, while doing research at the University of Chicago’s Medical School, conducted research on about 200 kinds of food, including several types of liquors, from all over the world in search of natural substance that could dissolve and even prevent blood clots. He found that Natto had the highest fibrinolytic activity among all those foods tested. In 1986, Dr. Sumi presented the results of his research in Japan for the first time.

Natto has a long cultural history, extending back more than 1,000 years and is made from boiled and fermented soybeans with a special bacterium, *Bacillus subtilis natto*, which gives natto a distinct and enjoyable flavor. Traditionally, it was also used as a folk medicine for heart and vascular diseases, to relieve fatigue and as an anti-atherosclerotic agent. Dr. Sumi said of Nattokinase, that it "shows a potency matched by no other enzyme." Nattokinase is extremely stable to variations in temperature, and acid and alkali milieu. Currently, Nattokinase has been the subject of 17 research studies, including two small human trials. In one such study, thrombi were induced in dogs, who were either given Nattokinase or placebo. Angiogram confirmation showed that the dogs who received the enzyme regained normal circulation within five hours of treatment, whereas, the placebo group continued to have demonstrable evidence of thrombus occlusion even after eighteen hours. In another study done in Japan to compare Nattokinase’s and Plasmin’s ability to dissolve thrombus in the carotid arteries of rats, animals treated with the Nattokinase regained 62% of their blood flow, whereas, the animals treated with Plasmin regained 15.8% of their blood flow.

**Nattokinase’s (NK) Effect on Fibrin/Blood Clots**

Fibrin is a protein that when activated forms fibrinogen, which is responsible for blood clotting. This is an important and protective mechanism that protects the body from excessive bleeding, say, when you cut yourself. However, in many instances, this process becomes over-activated or becomes “stuck” in high gear. This dysregulation of clotting has been implicated in a variety of serious health conditions, namely, cardiovascular disease (see table 1.2). The magnificent thing about Nattokinase is that it appears to have many, if not most, of the benefits of pharmaceutical agents designed to regulate blood clotting (e.g. warfarin, heparin, t-PA, urokinase, etc.) without any of the side effects of these medications. Furthermore, while these medications have to be injected and only provide a very brief time of benefit (a few hours), Nattokinase is effective when taken orally and its benefits linger many times longer. Standard doses of Nattokinase vary from 250-1,000 mg and positive effects can be seen with as little as 50 mg.

Fibrinolytic enzymes, which break down fibrin and thrombi, are normally generated in the endothelial cells. As the body ages, production of these enzymes begins to decline, making blood more prone to coagulation. Since these cells exist throughout the body, such as in the arteries, veins and lymphatic system, poor production of thrombolytic enzymes can lead to the development of clotting-prone conditions virtually anywhere in the body. This hypercoagulability has been linked to a variety of conditions, as seen in table 1.2.

Underlying connective tissue weakness due to nutritional deficiencies and dysfunction of the endothelium gives rise to inflammatory and repair mechanism. Once initiated, this pro-inflammatory/pro-oxidative process is not only the underlying process of atherosclerosis and vascular dysfunction, but also causes a propensity to thrombi and thromboemboli. More than 50 important substances that affect blood coagulation have been found in the blood and tissues, some of which are pro-

---

**ENERGEMS**

Imagine your electricity being healthy, simply with one ENERGEM.

Also neutralizes microwaves, geopathic stress, metal roofs, electrically transmitted & atmospheric toxins. Models for: CELL PHONES • HOME & OFFICE • SELF PETs • FOOD & PERSONAL ITEMS

ENERGETICS INTERNATIONAL, INC.
P.O. Box 6097 • Springfield, Virginia, VA 22150
Phone: 570-923-8696 • Fax: 570-921-5997
Toll Free: 866-815-0656 www.energems.com

TOWNSEND LETTER for DOCTORS & PATIENTS – NOVEMBER 2002 91
coagulants and some of which are anticoagulants. In general, however, once damage has occurred to the blood and blood vessels, the process of coagulation and clotting involve the following: Damaged, weakened or traumatized blood vessel or blood vessel wall, as initiated by nutritional deficiencies, trauma, and/or infection (can be chronic or acute) → Prothrombin Activator → Catalyzes the conversion of prothrombin to thrombin → Thrombin acts as an enzyme to convert fibrinogen into fibrin fibers → Fibrin fibers cause cloting. The final clot is composed of a meshwork of fibrin fibers, running in all directions and entrapping blood cells, platelets and plasma. Normally, the body has its own anti-coagulants, which are able to keep balance between the pro-coagulants, allowing for repair and healing, but not overshooting to cause pathological mechanisms. However, chronic nutritional deficiencies, infection, cell senility, and/or trauma can overwhelm the body’s endogenous coagulation homeostasis, resulting in thrombus or emboli. Although it is extremely important to treat the underlying cause, such as replenishing the necessary nutritional factors to allow for the formation and repair of healthy connective tissue and to support proper endothelial function, often immediate and acute modulation of a decompenated clotting system is needed. Until now, the only tools available to target a decompenated clotting system were potent pharmaceutical agents (“clot busters”) with known serious side effects. Now, however, an ideal candidate appears to be Nattokinase, which can safely accomplish this task in many instances.

While the human body contains several enzymes that promote the creation of blood clots, it only produces one that can dissolve clots (Plasmin), and the production of that enzyme diminishes as we age. It is interesting to note that oral Nattokinase (NK) in this study was more effective than Plasmin in dissolving thrombi. Research indicates that the mechanisms of Nattokinase stems from its close resemblance to endogenous plasmin; it appears to be able to dissolve fibrin directly and it may enhance the body’s own production of plasmin. Furthermore, Nattokinase appears to have ACE (Angiotensin Converting Enzyme) Inhibitor activity and in studies has been able to lower Systolic Blood Pressure up to 11% and diastolic pressure up to 9.7%.

Nattokinase produces a prolonged action (unlike antithrombin drugs that wear off shortly after IV treatment is discontinued) in two ways: it prevents coagulation of blood and it dissolves existing thrombus. Both the efficacy and the prolonged action of NK can be determined by measuring levels of EFA (euglobulin fibrinolytic activity) and FDP (fibrin degradation products), which both become elevated as fibrin is being dissolved. By measuring EFA & FDP levels, activity of NK has been determined to last from 8 to 12 hours. An additional parameter for confirming the action of NK following oral administration is a rise in blood levels of t-PA antigen (tissue plasminogen activator), which indicates a release of t-PA from the endothelial cells and/or the liver.

**Exciting Research**

Dr. Sumi and his colleagues induced blood clots in male dogs, then orally administered either four capsules of Nattokinase (250 mg per capsule) or four placebo capsules to each dog. Angiograms (X-rays of blood vessels) revealed that the dogs who received Nattokinase regained normal blood circulation (free of the clot) within five hours of treatment. Blood clots in the dogs who received only placebo showed no sign of dissolving in the 18 hours following treatment. Researchers from Biotechnology Research Laboratories and JCR Pharmaceuticals Co. of Kobe, Japan, tested Nattokinase’s ability to dissolve a thrombus in the carotid arteries of rats. Animals treated with Nattokinase regained 62% of blood flow, whereas those treated with plasmin regained just 15.8% of blood flow. Another research team from JCR Pharmaceuticals, Oklahoma State University, and Miyazaki Medical College tested Nattokinase on 12 healthy Japanese volunteers (6 men and 6 women, between the ages of 21 and 55). They gave the volunteers 200 grams of natto (the food) before breakfast, then tracked fibrinolytic activity through a series of blood plasma tests. The tests indicated that the natto generated a heightened ability to dissolve blood clots: On average, the volunteers’ ELT (a measure of how long it takes to dissolve a blood clot) dropped by 48% within two hours of treatment, and volunteers retained an enhanced ability to dissolve blood clots for 2 to 8 hours. As a control, researchers later fed the same amount of boiled soybeans to the same volunteers and tracked their fibrinolytic activity. The tests showed no significant change.

**Conclusion**

Nattokinase appears to have the added benefit of significantly reducing elevated blood pressure (an often concomitant condition in cardiovascular disease risk factors, such as high fibrin). Nattokinase appears to be safe, and has been used for over 1,000 years safely with no reports of toxicity. Various other nutritional supplements/herbs have been reported to have fibrinolytic activity, however, the potency of Nattokinase appears to be superior (see table 1.3). Furthermore, Nattokinase also appears to be an activator of various other metabolic enzymes and vitamins, cleaving them from their inactive to their active forms. The strength and magnitude of this direct support for the metabolic enzymes of the body, from an oral enzyme supplement, is unique to Nattokinase and shows great promise as a nutritional supportive agent in exciting and diverse ways. The potent fibrinolytic enzyme Nattokinase appears to be safe based upon the long-term traditional use of this food. Nattokinase has many benefits including convenience of oral administration, confirmed efficacy, prolonged effects, cost effectiveness, and it can be used preventively. It is a naturally occurring, food based dietary supplement, being marketed in this country by innovative nutriceutical companies and has demonstrated stability in the gastrointestinal tract, as well as to changes in pH and temperature. Truly, Nattokinase represents a quantum leap forward in the future of enzymology and a new chapter in dietary supplements.

Nicholas Calvino, DC is a Nutritional Consultant, Master Herbalist Candidate and is a noted author and lecturer on the subject of health and nutrition. His company, Natural
Enzyme of Enzymes


ISBN: 3-609-51280-6


References
Allergy Research Group Nutraceuticals, Clinical Focus Newsletter, August 2002. www.allergyresearchgroup.com


Doctor: Are you treating any of the 56 million Americans who suffer from IBS? They need to take BowelSoothe™ because it is clinically proven to effectively manage their symptoms.

BowelSoothe, dispensed in China for the last 15 years, continues to be the first line of treatment for IBS. A serving of BowelSoothe provides 10 grams of ultraconcentrated White Peony Root, Atractylodes Rhizome, Cardamom Seed, Paederia scandens Stem, Sonchus brachyotus Entire Plant and Licorice Root (DGL). BowelSoothe is 100% natural and 100% drug free.

Want more information? Visit our website at www.bowelsoothe.com. To order BowelSoothe or to request more information, please call us toll free at: 888-686-3683.

(Outside the USA, call: 949-589-3646)

1 Chinese Journal of Internal Medicine 1997;3(1):30
2 Hua Xi Medical Journal 2000, 15(6):432
3 Assays available upon request