Focus

Allergy Research Group® Newsletter January 2003

In This Issue

Allergy Research Group®

Hypercoagulation Linked to Chronic Fatigue, Fibromyalgia, MS, Infertility, Chronic Illness

The following is a brief summary of the work of David Berg of Hemex Laboratory in Phoenix, Arizona, linking an immune-activated hypercoagulation mechanism to a wide range of chronic conditions.

Immune System Activation of Coagulation (ISAC): Chronic Illnesses Due to a Coagulation Protein Defect

Infertility (Recurrent Fetal Loss), TIA, Osteonecrosis of the Jaw, Chronic Fatigue Syndrome/Fibromyalgia (CFS/FM), Crohn's Disease, IBD, Multiple Sclerosis, Sjogren's Syndrome, Lyme Disease

The Model - A Paradigm Shift

The model proposes that a majority of individuals diagnosed with chronic illnesses, based on clinical criteria, may be potentially classified as "Anti Phospholipid Antibody Syndrome" (APS) with the endothelial cell (EC) as the disease target. **These patients have a hypercoagulable state demonstrated by increased markers of coagulation activation and increased blood viscosity due to the generation of Soluble Fibrin Monomer (SFM)**. The CFS/FM process may be triggered by a variety of pathogens

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Potent Natural Anticoagulant Enzyme Derived From Traditional Japanese Food

"In all my years of research as a professor of cardiovascular and pulmonary medicine, natto and nattokinase represents the most exciting new development in the prevention and treat - ment of cardiovascular related diseases" - Martin Milner, N.D.

Nattokinase is a potent fibrinolytic enzyme extracted and highly purified from a traditional Japanese food called Natto. Natto is a fermented cheese-like food that has been used in Japan 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 bacteria, to boiled soybeans. The resulting nattokinase enzyme, is produced when Bacillus natto acts on the soybeans. **While other soy foods contain enzymes, it is only the natto preparation that contains the specific nattokinase enzyme.**

The Discovery of Nattokinase

Doctor Hiroyuki Sumi had long researched thrombolytic enzymes searching for **a natural agent that could successfully dissolve thrombus associated with cardiac and cerebral infarction (blood clots associated**

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Hypercoagulation *continued*

(CMV, HHV6, Mycoplasma, Chl. pneumonia, etc.), resulting in pathogen-mediated immune activation that induces antibodies which cross-react with EC protective proteins B2GPI & Annexin V. These antibodies dislodge the protective proteins from EC surfaces, exposing PhosphatidylSerine (PS) on the EC surfaces in capillary beds. Pathogens induce inflammatory responses which include cytokine modulation of EC to down-regulate the antithrombotic environment (Thrombomodulin, tPA) in favor of prothrombotic expression of Tissue Factor (TF). TF and PS exposure allows binding of the coagulation tenase and prothombinase complexes to EC surfaces. **This results in thrombin generation leading to SFM formation. SFM dimerizes easily, increasing blood viscosity and precipitating out on EC surfaces as fibrin(oid) deposition, creating local ischemia and pathology, blocking nutrient and oxygen delivery in the microcirculation.** A hereditary defect in a coagulation regulatory protein, such as protein C, protein S, Factor VL, prothrombin gene mutation, PAI-1, Lp(a), or elevated homocysteine is predispositional in greater than 75% of patients. Because this hypercoagulability does not result in an immediate thrombosis (100% occlusion), but rather in fibrin deposition (50-95%), we suggest that an appropriate name for this antiphospholipid antibody process to be **Immune System Activation of Coagulation (ISAC) syndrome. This model provides an explanation for the therapeutic benefits reported with low dose anticoagulant therapy (heparin or warfarin) in the majority of chronically ill patients.**

People are not chronically ill unless there is a coagulation regulatory protein defect as seen in Thrombophilia or Hypofibrinolysis. ■

For more information on lab assessment and therapeutic protocols visit the Hemex Laboratory website at: www.hemex.com.

Detoxification of Biotoxins in Chronic Neurotoxic Syndromes

Patricia Kane, Ph.D.

"Patients are reporting that they have more energy, less pain and a clearing of mental confusion in the first few days of using nattokinase!"

The following is an excerpt from the work of Neal Speight, M.D., John Foster, M.D., and Patricia Kane, Ph.D. who have established a medical protocol to treat chronically ill patients who are suffering from hypercoagulable states related to neurotoxin exposure. The patient population affected includes those with CFS, Fibromyalgia, MS, Cardiovascular Disease, Depression, Rheumatoid Arthritis, IBS, Infertility, Lyme , Stroke, Toxic Building Syndrome, Estuary Associated Syndrome, Diabetes without family history, Optic Neuritis, Refractory Heavy Metal Toxicity, Pulmonary Hemorrhage. Patients diagnosed with these chronic illnesses may be potentially classified as 'Neurotoxic Membrane Syndrome' (NMS) with the endothelial cell membrane as the target of degeneration. While hypercoagulation involves a myriad of proteins, it is ultimately a membrane event, essentially disrupting the phospholipids that structure the membrane. Agglomeration (blocked cellular exposure to blood flow / nutrients and impaired cell-to-cell communication) indicates elevation of phospholipase A2 and the uncoupling of eicosanoids from the cell membrane causing inflammation.

Neurotoxins are minute compounds that are comprised of oxygen, nitrogen and sulfate atoms arranged in such a way as to make the outside of the molecule fat loving and water hating. Once a neurotoxin enters the body, it tends to bind to structures that are rich in fat such as most of our cells, especially in the liver, kidneys, and brain. Neurotoxins are capable of dissolving in fatty tissue and moving through it, crossing cell membranes, and transporting against a gradient, particularly with potassium, disrupting the electrical balance of the cell itself.

As fat soluble neurotoxins move through the cells of the body, they eventually enter the liver and the bile. Once neurotoxins bind with bile they have access to the liver, and the body is poisoned over and over again as the bile is re-circulated.

Neurotoxins cause damage by disrupting sodium and calcium channel receptors, attacking enzyme reactions involved in glucose production thereby disrupting energy metabolism in the cell, manufacturing renegade fatty acids as saturated very long chain, odd chain and branched chain fatty acids impairing membrane function, stimulating enzymes (PLA2) which uncouple essential fatty acids from the cell membrane and impairing the function of the nuclear receptor PPAR gamma which controls transcription (the conversion of instructions held in our DNA to RNA which then leads to translation or protein production in the cell).

Once neurotoxins get into the cell they move toward the nucleus turning on indirectly the production of cytokines such as TNF alpha, IL6, and IL-1 Beta. TNF alpha will cause the garbage cells in the body (macrophages) to become active. The white cells are also induced to gather in the area of the cytokine (TNF alpha) release. TNF alpha also induces endothelial cell adhesion. Endothelial cells which line the blood vessels of the body become "sticky" in conjunction with the increase in white cells. Increased blood viscosity results in restricted blood flow in neurotoxic patients leading to fatigue and discomfort.

Hypercoagulation is predominantly an unwanted mass of proteins disrupting function. When referencing the artery,

Continued next page

Biotoxins *continued*

hypercoagulation invariably involves the plasmic side of the cell and if endothelial cells of the vascular system are targeted by a toxin (virus, neurotoxin, metal, antibody, etc.), restriction of blood flow ultimately results. If a neuron is targeted then signaling is disrupted. The presence of neurotoxins involves PLA2, which monitors cell membrane health. A membrane disturbance (unwanted mass) would trigger the release of eicosanoids, which would then induce inflammation and call to attention the clean-up committee, i.e. macrophages.

Our approach is to first confirm that neurotoxin-mediated illness is in fact, a problem for the patient via the Visual Contrast Sensitivity test that isolates deficits in velocity of flow in retinal capillaries. If the patient scores poorly on this test then the evaluation may include screening for cytokine elevations followed by Coagulation and Red Cell lipid testing through BodyBio/Johns Hopkins.

We initiate treatment with changing the patients' overall diet, addressing the outer lipid leaflet of the cell membrane through fatty acid therapy and the addition of supplementation targeted towards dissolving fibrin, clearing the liver/biliary tree, and healing the cell membrane. The patients' progress is evaluated through the visual contrast test and repeat lab evaluation.

Additionally, binding therapy with the cholesterol lowering drug Cholestyramine is an option in treating some of these patients. This drug has a complimentary positive charge to the generally negative charge of the neurotoxin and as the neurotoxin-bile complex passes the Sphincter of Oddi where bile is released from the gallbladder, it binds neurotoxins linked to bile which can then not be reabsorbed. Prolonged use of Cholestyramine has proven to be disappointing in patient outcomes when the infection is of a chronic nature. Cycling of Cholestyramine has been utilized (5 days on, 10 days off) or an early AM single dose for several months.

We have found that venous Phospholipid Exchange is one of the most efficient ways of clearing the liver and biliary tree which are paramount in addressing neurotoxic syndromes. Oral use of phospholipids in a Liver Flush is also an effective intervention.

Blood thinning agents such as Heparin and Warfarin increase blood flow around the damaged endothelium, however, reconstituting membrane fluidity can directly address coagulation in a natural restorative way. Healthy membranes will not permit agglomeration. The high POLY unsaturated lipids with a preponderance of phosphatidylcholine on the plasmic surface precludes undesirable clumping to occur. Treatment modalities should address dissolving fibrin and healing the cell membrane.

Unhealthy bacteria have been known to colonize the liver and biliary system. These bacteria can synthesize very long chain saturated or renegade fats that lead to liver toxicity, biliary congestion and impairment of prostaglandin synthesis. When renegade fats are over represented in the cell membrane they result in off key expression, and if strong enough, may cause cellular death and apoptosis. Healing the outer leaflet of the membrane, comprised primarily of phosphatidylcholine, with phospholipid therapy, is our highest priority in addressing chronic illness and hypercoagulation. ■

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Nattokinase *continued*

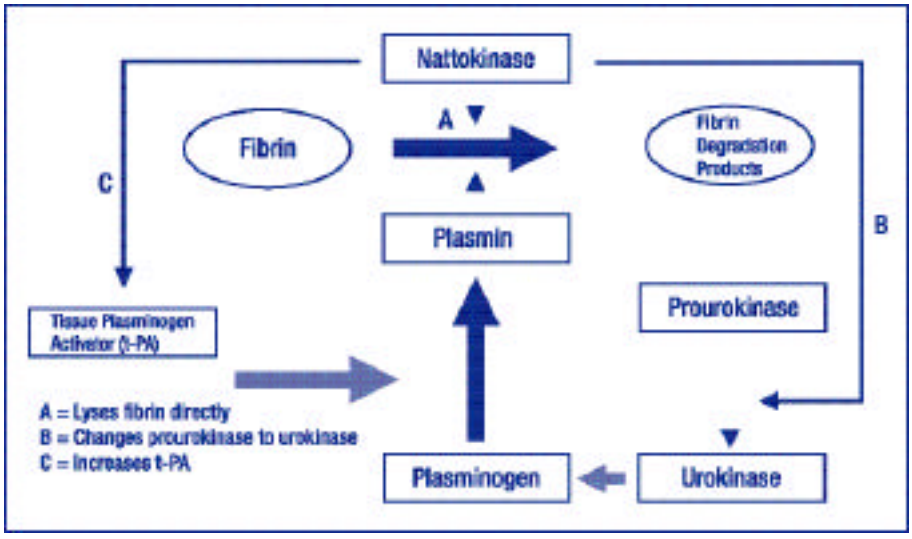
with heart attacks and stroke), and can degrade fibrin, which coagulates prior to full clot formation. Sumi discovered nattokinase in 1980 while working as a researcher and majoring in physiological chemistry at Chicago University Medical School. After testing over 173 natural foods as potential thrombolytic agents, Sumi found what he was looking for when Natto was dropped onto artificial thrombus (fibrin) in a Petri dish and allowed it to stand at 37 C (approximately body temperature). The thrombus around the natto dissolved gradually and had completely dissolved within 18 hours. Sumi named the newly discovered enzyme "nattokinase", which means "enzyme in natto". **Sumi commented that nattokinase showed "a potency matched by no other enzyme."**

Potent Thrombolytic Activity

The human body produces several types of enzymes for making thrombus, but only one main enzyme for breaking it down and dissolving it – plasmin. **The properties of nattokinase closely resemble plasmin.** According to Dr. Martin Milner, from the Center for Natural Medicine in Portland, Oregon, **what makes nattokinase a particularly potent treatment, is that it enhances the body's natural ability to fight blood clots in several different ways, because it so closely resembles plasmin and it dissolves fibrin directly. In addition, it also enhances the body's production of both plasmin and other clot-dissolving agents, including urokinase (endogenous).** "In some ways", Milner says, "nattokinase is actually superior to conventional clot-dissolving drugs. T-PAs (tissue plasminogen activators) like urokinase (the drug), are only effective when taken intravenously and often fail simply because a stroke or heart attack victim's arteries have hardened beyond the point where they can be treated by any other clot-dissolving agent. **Nattokinase, however, can help prevent that hardening with an oral dose of as little as 100 mg a day." This may be very important because the fibrin accumulation associated with endothelial cells can eventually interfere with oxygen and nutrient transfer to body cells and removal of waste products. Hence, fibrin accumulation on the vascular endothelial lining interferes with the primary functions of the blood and may be a critical factor in aging. We think that by clearing fibrin from the vascular endothelial cells, nattokinase may function as an anti-aging enzyme, that has heretofore been unavailable to physicians.**

The Physiological Effects of Nattokinase on Fibrin

Nattokinase lyses fibrin directly (A), changes prourokinase to urokinase (B), and increases tissue plasminogen activator (t-PA)



The Prolonged Action of Nattokinase

Nattokinase produces a prolonged action (unlike antithrombin drugs that wear off shortly after IV treatment is discontinued) in two ways: it enhances the body's endogenous fibrinolytic activity 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 TPA antigen (tissue plasminogen activator), which indicates a release of TPA from the endothelial cells and/or the liver.

The Mechanism Behind Thrombus

Blood clots (or thrombi) form when strands of protein called fibrin accumulate in a blood vessel. In the heart, blood clots cause blockage of blood flow to muscle tissue. If blood flow is blocked, the oxygen supply to that tissue is cut off and it eventually dies. This can result in angina and heart attacks. Clots in chambers of the heart can mobilize to the brain. In the brain, blood clots also block blood and oxygen from reaching necessary areas, which can result in senility and/or stroke.

Thrombolytic enzymes are normally generated in the endothelial cells of the blood vessels. **As the body ages, production of these enzymes begins to decline, making blood more prone to coagulation and fibrin accumulation in the vascular endothelium.** Eventually, this mechanism can lead to cardiac or cerebral infarction, as well as other conditions. **Since endothelial 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 thrombotic conditions virtually anywhere in the body.**

It has recently been revealed that **coagulative clogging of the cerebral blood vessels may be a cause of dementia.** It has been estimated that sixty percent of senile dementia patients in Japan is caused by thrombus. Thrombotic diseases typically include cerebral hemorrhage, cerebral infarction, cardiac infarction and angina pectoris, and also include diseases caused by blood vessels with lowered flexibility, including senile dementia and diabetes (caused by pancreatic dysfunction). Hemorrhoids are considered a local thrombotic condition. If chronic diseases of the capillaries are also considered, then the number of thrombus related conditions may be much higher. Cardiac infarction patients may have an inherent imbalance in that their thrombolytic enzymes are weaker than their coagulant enzymes. Nattokinase holds great promise to support patients with such inherent weaknesses in a convenient and consistent manner, without side effects such as increased bleeding.

Research In The United States

Dr. Martin Milner of the Center for Natural Medicine in Portland, Oregon and Dr. Kouhei Makise of the Imadeqawa Makise Clinica in Kyoto, Japan were able to launch a joint research project on nattokinase and write an extensive paper on their findings. **"In all my years of research as a professor of cardiovascular and pulmonary medicine, natto and nattokinase represents the most exciting new development in the prevention and treatment of cardiovascular related diseases," Dr. Milner said. "We have finally found a potent natural agent that can thin and dissolve clots effectively, with relative safety and without side effects."**

Animal & Human Studies

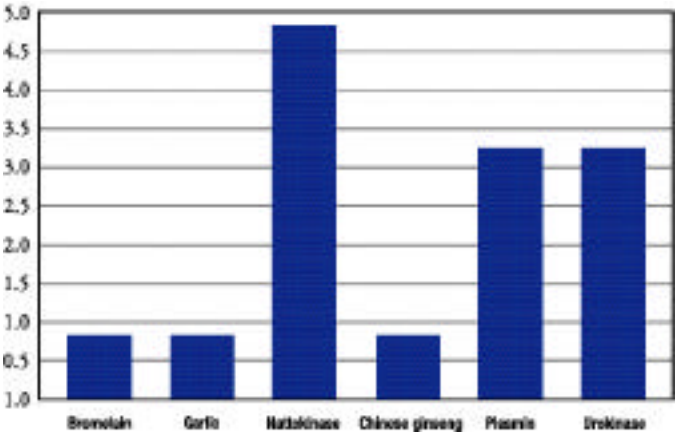
Nattokinase has been the subject of 17 studies, including two small human trials:

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 percent of blood flow, whereas those treated with plasmin regained just 15.8 percent of blood flow.

Researchers 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 percent 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.

Comparison of Commonly Used Fibrinolytic Agents



The Benefits of Nattokinase on Blood Pressure

Traditionally in Japan, Natto has been consumed not only for cardiovascular support, but also to lower blood pressure. In recent years, this traditional belief has been confirmed by several clinical trials. In 1995, researchers from Miyazaki Medical College and Kurashiki University of Science and Arts in Japan **studied the effects of nattokinase on blood pressure in both animal and human subjects** (see below). In addition, the researchers confirmed the presence of inhibitors of angiotensin converting enzyme (ACE), which converts angiotensin I to its active form angiotensin II within the test extract, which consisted of 80% ethanol extract of lyophilized viscous materials of natto. ACE causes blood vessels to narrow and blood pressure to rise - by inhibiting ACE, nattokinase has a lowering effect on blood pressure.

Animal Study

After a single intraperitoneal administration of the test extract (equivalent to 25 mg of natto food) into male Wister rats, systolic blood pressure (SBP) significantly decreased from 166 + mmHg to 145 + 24 mmHg in just two hours ($p<0.05$), and decreased further to 144 + 27 mmHg in 3 hours ($p<0.05$). On average, this data represents a 12.7 percent drop in SBP within two hours.

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Opinions of Experts

NATTOKINASE

Patricia Kane, Ph.D.

"I started 25 patients on nattokinase last week in our clinic and patients are reporting that they have more energy less pain and a clearing of mental confusion in the first few days of use! We have already added nattokinase into our medical protocol for detoxification of neurotoxins."

Patricia Kane, Ph.D.

Editor: Do you feel that individuals using nattokinase who are not on a comprehensive therapeutic program may run a risk of circulating existing infections?

Dr. Kane: No, I think nattokinase is overall a safe intervention. However, in our clinic we would not exclusively use nattokinase, but rather implement a comprehensive nutrient base at the same time. Some clinicians may attempt to just use the nattokinase without other nutrient support such as fatty acid therapy. I do not think this would be harmful but they may not achieve the same degree of response we have had with patients in our clinic who have had the opportunity to optimize membrane function.

Jonathan Wright, M.D.

"The literature about natto and nattokinase is very impressive. The first patient we asked to try it had a rapid and dramatic response. While this was likely an unusually good result, nattokinase appears to be a true therapeutic breakthrough."

Jonathan Wright, M.D.

Betty Kamen, Ph.D.

"Because of our deep involvement in the nutrition field, my husband and I are aware of a long list of helpful, natural, and safe modalities for recovery from illness - regardless of the disease category. Many of these substances worked well for my husband's recent problem, but nothing appeared as magical as nattokinase! In terms of his energy and well-being, it was as though a switch was suddenly turned on when he started taking this amazing supplement. The positive effects of nattokinase are swift and dramatic!"

Betty Kamen, Ph.D.

Betty Kamen introduced us to nutrition concepts more than fifty years ago. She has written 20 popular nutrition books, hundreds of articles, and has done extensive work as host and guest on radio and TV. Betty offers a free, on-line, daily nutrition hint. (To subscribe, just email to betty@well.com and write "Hint" in the subject area, or go to her website at www.bettykamen.com.) Betty is still letting us know about innovative supplements. The above is her recent personal experience with nattokinase.

Ralph E. Holsworth, Jr., D.O. on Safety

"After reviewing the Single Oral Dose Toxicity Study of Nattokinase Powder in Rats dated February 26, 1999 (see page 9), I extrapolated the dose a 70 kilogram human would receive from the 2000 mg per kg of body weight dose administered to the animals. Each animal was given 20,000 FU per kg of body weight, or a dose equivalent to 1,400,000 FU for a 70 kg human, or *700 times* the recommended daily dose of nattokinase (i.e., 2,000 FU per day as suggested by Dr. Sumi). An FU is a fibrin unit or activity unit that quantifies the enzyme's ability to lyse or "cut" fibrin in vitro. Activities allow us "to compare apples to apples and oranges to oranges." I am convinced that the study performed on behalf of Japan BioScience Laboratories indicates that nattokinase is extremely safe!"

"I have also received preliminary verbal reports from a similar acute toxicity study with nattokinase of twice the activity (20,000 FU per gram) and no toxicity in the animals has been reported. The Japanese researchers concluded that an inactive ingredient removed in the refinement process for manufacturing the nattokinase was responsible for the soft stools and diarrhea. It would be interesting to compare this acute toxicity test of nattokinase with another food or dietary supplement to illustrate the safety and extreme low toxicity."

Ralph E. Holsworth, Jr., D.O. (nattokinase researcher)

Opinions of Experts

Stephen Levine, Ph.D. on Safety

Our reflections on the potential safety of natural anticoagulants generally is this: Any natural agent that improves blood flow should improve health. However, most deep healing modalities will often bring to the surface certain symptoms, though usually superficial. A good example of this is homeopathy, which heals from the inside out, and sometimes causes skin conditions by releasing toxins to the surface. Clinical symptoms associated with homeopathic healings are common. The Herxheimer reaction can be associated with the use of natural or synthetic antibiotics / antimicrobials as toxicity associated with pathogen "die off" and can cause acute clinical symptoms. The Herxheimer reaction is a good indication that microbical die off is occurring and is a sign of healing of infections, which can be bacterial, viral, fungal, or parasitic in nature.

So what can we expect from the use of natural anticoagulative support? We would expect that certain pathogens which hide in the fibrin and / or may be localized, may be exposed or circulated as fibrin is degraded, and as blood flow and hemodynamics is improved. This then may present some immune challenge for debilitated patients. We may expect that associated with improved circulation, immune challenge may develop and release toxins, which is basically a Herxheimer type reaction.

Surprisingly, though the use of nattokinase is extremely safe based upon historical use of Natto and animal studies of nattokinase, the recent acute toxicity study of nattokinase using **700 TIMES** the physiological dose for humans, caused no toxicity in rodents. The remarkable safety and lack of side effects in animal studies at these enormous doses, and the safety in humans from traditional use of Natto appears to be related to the observation that Natto and nattokinase is self-regulating / limited and does not cause bleeding in excess, as does heparin and coumadin. These drugs cause extreme blood thinning, and potentially, excess bleeding, if not tightly regulated.

One may comment that there was no interview of the rodents, or screening of the subtle effects of nattokinase. However, the lack of toxicity from enormous doses of nattokinase, strongly argues for the safety of the agent.

Martin Milner, N.D. on Safety

The following is a brief summary of material regarding the safety of nattokinase from *Natto and Its Active Ingredient Nattokinase: A Potent and Safe Thrombolytic Agent* by Martin Milner, N.D. and Kouhei Makise, M.D., which appeared in the June 2002 issue of Alternative & Complimentary Therapies.

Safety in General

Animal studies have shown that nattokinase is completely safe and nontoxic. According to unpublished studies, acute oral toxicity studies show that extremely high doses of nattokinase are not lethal to rats. From Dr. Makise's personal correspondence with Dr. Hiroyuki Sumi, Sumi emphasized that Japanese people have been eating natto as part of their diet for many years with no known side effects or complications.

Drug Interactions

The nattokinase in natto could require healthcare providers to lower patients' doses of Coumadin. It is necessary to take a consistent amount of natto / nattokinase each day when accompanied by other drugs. Physicians also need to monitor clotting time (PT, PTT, and international units normalizing ratio levels) in the first weeks of natto or nattokinase therapy until these levels are stable.

Conclusion

Natto extracts with significant amounts of nattokinase are promising functional foods. All prior epidemiologic and clinical research points to nattokinase's effectiveness and safety for managing a wide range of diseases. Evidence from long-term use at high doses in Japanese people points to nattokinase as a safe nutrient.

NATTOKINASE

Nattokinase *continued*

Human Study

The same natto extract was then tested on human volunteers with high blood pressure. Blood pressure levels were measured after the extract (equivalent to 200 grams of natto food) was administered orally for 4 consecutive days. In 4 out of 5 volunteers, the systolic blood pressure (SBP) decreased on average from 173.8 + 20.5 mmHg to 154.8 + 12.6 mmHg. Diastolic blood pressure (DBP) decreased on average from 101.0 + 11.4 mmHg to 91.2 + 6.6 mmHg. **On average, this data represents a 10.9 percent drop in SBP and a 9.7 percent drop in DBP**.

Conclusion

The traditional Japanese food Natto has been used safely for over 1000 years. 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 can be used preventatively. It is a naturally occurring, food based dietary supplement that has demonstrated stability in the gastrointestinal tract, as well as to changes in pH and temperature.

As indicated by David Berg, we suspect that sticky blood caused by immune activation and coagulation processes, may be a common occurrence in diverse degenerative pathologies. Natural agents such as nattokinase, which directly degrade fibrin, prevent its formation, and degrade clots, may have very broad applications in achieving optimum health.

It is interesting, that with the discovery of the importance of gut permeability problems and dysbiosis, many came to understand that for optimal nutrient absorption, the gut wall could potentially be a major barrier. But here, we are suggesting that broad ranging stressors leading to fibrin accumulation at the intima of the vascular endothelial cells, may harbor pathogens and block nutrient and oxygen flow to the cells, as well as block the elimination of toxins, with increased inflammation and immune activation, thereby constituting a significant portion of aging and/or chronic illness. Therefore, nattokinase may be a valuable enzyme for cleaning the vessels, and optimizing the function of the blood. ■

Glossary of Terms

Fibrin: A whitish, filamentous protein formed by the action of thrombin on fibrinogen and makes up part of coagulum or blood clots.

Fibrinolytic: Pertaining to or causing the breaking up of blood clots.

Plasmin: An endogenously produced fibrinolytic enzyme.

Plasminogen: A precursor to plasmin. A protein found in many tissues and body fluids.

Thrombolytic: Pertaining to or causing the breaking up of a thrombus.

TPA: Tissue plasminogen activator.

t-PAs: The most commonly used thrombolytic drugs including activase, urokinase, and streptokinase.

Urokinase: An endogenously produced thrombolytic enzyme & also a commonly used thrombolytic drug given intravenously to cardiac and cerebral infarction patients.

Further suggested reading: *Natto: A Soy-Based Supplement for Enhancing Heart and Circulatory Health* by Dr. Martin Milner in the June 2002 issue of Alternative & Complementary Therapies.

References available on request.

These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

Lumbrokinase: Another Potent Fibrinolytic Agent

The Use of Lumbrokinase in Cardiovascular Medicine in China

Lumbrokinase (LK) consists of a group of proteolytic enzymes including plasminogen activator and plasmin extracted from a specific species of earthworm. The plasminogen activator (e-PA) in LK is similar to tissue plasminogen activator (t-PA) from other sources, which makes it possible to show the thrombolytic activity only in the presence of fibrin. Therefore, LK has the advantage of not causing excessive bleeding. The activity of LK is much higher than most traditional Chinese medicines that are available in the United States. Four phases of clinical studies have been done on LK at the Beijing Xuanwu Hospital (the top hospital in nerve & internal medicine in China). **LK has been widely used in over 100 hospitals in Beijing since 1995. In Jakarta, LK has been used in thousands of hospitals and drug stores in more than 20 provinces and cities as well as in Hong Kong, Taiwan, Southeast Asia, and Europe.**

LK has a certificate of GMP for human drugs from the SDA in China and is recognized as a state class new drug approved by the Ministry of Public Health. LK capsules technology was awarded with a certificate of National Significance Achievement in Science and Technology listed as the Promotional project of National Key Technology Achievement and the National Torch Plan Program, and selected as National Key New product by 6 major ministries. It has been included in the Medicines Catalog of National Fundamental Health Insurance and awarded with gold price at China's Achievement in Medicine and Public Health Technology Fair.

**More on lumbrokinase in our next newsletter.*

Acute Toxicity Animal Study Demonstrates Nattokinase Safety at Approximately 700 Times the Recommended Human Dose

Single Oral Dose Toxicity Study of Nattokinase Powder in Rats
Japan BioScience Laboratory, February 26, 1999

A study was performed to assess single oral dose toxicity of the test material - nattokinase powder containing 10,000 FU (fibrinolysis units) per gram, in Sprague-Dawley rats. This study was based on the recommendations of the "Standard of the enforcement of non-clinical test regarding the safety of drugs" (Notification No. 21 of the Pharmaceutical Ministry of Health and Welfare, March 26, 1997, Japan). The method of the study was conducted in accordance with "The guidelines for the toxicity study of drugs" (No. 88 of Yakushinyaku, August 10, 1993, Japan). One group of five male and five female rats were given a single oral dose of the test material at a dose of 2000 mg per kg body weight (approximately 700 times the daily human dose recommended by Dr. Sumi). The animals were observed for 14 days after the day of dosing. All animals were subjected to gross pathological examination at the end of the study.

Results:

1) No abnormalities were observed in all animals at necropsy.

2) No deaths occurred for the study period.

3) Diarrhea in 2 males and soft stools in 3 males were detected at one day after dosing; soft stools in all 5 females was detected at one day after the dosing, but no abnormalities were detected on the other observation days.

4) Normal body weight gains were noted for all animals in the study period.

New Acute Toxicity Study Just Completed Using Test Material Double the Potency & Purity As Above

Oral Repeated Dose 28-Day Toxicity Study of Nattokinase in Rats
Kobuchisawa Laboratories, Fuji Biomedix Co., Ltd.
Sponsored by Japan BioScience Laboratory, August 8, 2002

A new 28-day oral repeated dose toxicity study has just been completed using a test material double the potency and purity as the above test material (20,000 FU per gram instead of 10,000 FU per gram).

Summary of the Results:

Sprague-Dawley rats (6 males & 6 females), were administered nattokinase orally at dose levels of 0 (control) and 167 mg/kg/day for 28 days to examine toxicity of the test substance containing 20,000 FU (fibrinolysis units) per gram. Animals were observed for clinical signs and subjected to body weight and food consumption measurements, urinalysis, and ophthalmological examination. At the end of the treatment period, animals were subjected to hematological, blood chemical, and pathological examinations. No changes attributable to treatment were found in any parameter examined. Consequently, 167 mg/kg/day is considered to be a no effect level for toxicity in the present oral repeated-dose 28-day study of nattokinase in rats.

Nattokinase & Vitamin K: Reason to be Aware

Most forms of nattokinase contain vitamin K, which is strictly contraindicated for patients using Coumadin, Heparin, and other blood-thinning medications, as it may cause blood clots. There are a number of manufacturers of nattokinase in Japan which produce product of varying grades of purity and potency. One supplier holds a U.S. patent on a sophisticated vitamin K removal process. In addition, this process also removes Bacillus spores (the microbe used during fermentation), which can remain in other nattokinase products, especially if vitamin K has not been removed.

Vitamin K Removal Process

The Bacillus natto culture is treated with chitosan, and then filtered, concentrated, and dried. According to this method, a Bacillus natto culture extract containing nattokinase and 1 mcg or less of vitamin K2/g dry weight is obtained.

Bacillus Natto Only

Nattokinase is a unique enzyme only sourced from the fermentation of soybeans by Bacillus natto and by no other microbes and/or fungi. All clinical and scientific research is solely based upon natto and nattokinase derived by Bacillus natto.

Interview *with* David Berg

David Berg is the Director and Cofounder, with Lois Hill Berg, of HEMEX Laboratories. Along with Dr. Harold Harrison and several clinical collaborators, they have developed the idea of the hypercoagulation/immune system activation of coagulation theory in chronic diseases, a proposed cause of Chronic Fatigue Syndrome and Fibromyalgia, and have proposed an appropriate treatment that reduces many related symptoms. Mr. Berg has a M.S. degree in clinical pathology and laboratory medicine, and has been in practice for 35 years. HEMEX Laboratories offers testing and consultative services relating to the diagnosis, treatment, and monitoring of hematological, clotting and/or bleeding disorders.

Hypercoagulability and the Development of Chronic Illness

We first became involved with research in chronic illnesses while we were performing research regarding hypercoagulability-related infertility in women with one of the local infertility specialists here in Phoenix, AZ. We found that a hypercoagulable state, presumably due to a coagulation protein defect, existed in many women who were infertile and/or who had recurrent spontaneous abortions. Our colleague Dr. Couvaras observed that when he put women on low dose heparin in order to maintain pregnancy, some with CFS/FM-like symptoms, pelvic pain, and migraine-like headaches had amelioration of their symptoms. He asked us "Why?" As a result, we performed a retrospective study on 30 of these obstetric patients with chronic illness symptoms, and determined that all had coagulation system activation. As the hypercoagulability was decreased by heparin injections, the chronic illness symptoms diminished. This was the first clue to the connection between coagulation and chronic illnesses. These findings were published as a poster at the 1998 AACFS meeting in Cambridge, MA.

We subsequently refined our test panel for low level activation of coagulation to include Prothrombin fragment 1+2 (F1+2), thrombin/antithrombin complexes (T/AT) and Platelet Activation by Flow Cytometry assays. Thus, the ISAC or Immune System Activation of Coagulation panel consisting of fibrinogen (FIB), soluble fibrin monomer (SFM), F1+2, T/AT, and PA by Flow was born. With our partner and Medical Director, Dr. Harold Harrison and several clinical collaborators, we then designed and conducted a prospective, multi-center, blinded, case control, associative study of non-obstetric CFS/FM patients and controls, with centers in New York, Houston, and Phoenix. When the code was broken, identifying patients and controls, we were able to identify most of the CFS/FM patients based on having two or more positive test results out of the five assays in the ISAC panel. It was the first definitive evidence that, indeed, chronic illnesses have a demonstrable basis in the blood coagulation system. This study was published in the international journal Blood Coagulation & Fibrinolysis, 1999, 10:435-438. In another associative cohort study published in Blood Coagulation & Fibrinolysis, 2000, 11:673-678, we determined that Gulf War illness has similar findings of low level activation of coagulation.

In November, 1999, Dr. Joe Brewer (an Infectious Disease specialist in Kansas City) and I developed a model of pathogen activation of the immune and coagulation systems. The model proposes that the end result of such pathogen-mediated activation is increased blood viscosity due to 1) an underlying coagulation regulatory protein defect, and 2) activation of the coagulation system by the pathogen. As the blood viscosity increases, the diminished blood flow creates hypoxia (lack of oxygen) and nutrient deprivation within various areas of the body. This is like trying to start your car in Wisconsin in the winter with 60-weight engine oil. This model explains the multi-organ symptomatology and also explains why the low dose heparin therapy is effective by increasing blood flow as the blood viscosity decreases. Thus, patients gain relief from their symptoms with this therapy.

The model states that coagulation activation generates thrombin, which converts fibrinogen to soluble fibrin monomer (SFM). Soluble fibrin becomes deposited in the microcirculation (capillaries) as fibrin or fibrinoid-like deposition, blocking oxygen and nutrients transfer to parenchymal tissues. Many pathogens activate the immune system. These include viruses (such as EBV, CMV, HHV6 & others), bacteria (mycoplasma, chlamydia, borrelia, etc), fungi (such as candida), etc. These pathogens are anaerobes, i.e., they live and reproduce in an oxygen deprived cellular matrix or environment. That's why fibrin deposition becomes important to the survival of the pathogens because it produces decreased oxygen in cells and tissues. One of the biggest challenges to a clinician is to figure out what pathogens are present in the patient, and therefore the most appropriate therapies against these pathogens. The average CFS/FM patient may have anywhere from one to seven pathogens that need eradication.

Positivity of two or more tests in the ISAC panel occurs in more than 80% of all patients tested. However, the longer a patient has been ill (many years), the less activation is needed by the pathogens for survival, and therefore fewer tests may be positive. Someone who has been ill for 10 years or more may only have one test positive in the panel. The ISAC panel also works very well for monitoring anticoagulant therapy between 4-6 weeks after therapy has started. It indicates whether or not there is enough heparin being given to the patient, the overall patient improvement and the reaction of the body to the pathogens, such as a Herxheimer-like reaction (relapse from infections or reactivation of pathogens).

In addition to the pathogens that can activate the immune system, metals (e.g. mercury, lead, aluminum), exogenous toxins, chemicals, allergens, physical trauma, vaccinations, and/or biological warfare agents can also activate the immune system. This may lead to secondary infections, which may also trigger coagulation activation. If the coagulation mechanism does not shut down properly, then there is continued thrombin generation and soluble fibrin formation, resulting in increased blood viscosity and decreased blood flow.

When you look for a genetic basis in this model, one can test for seven different regulatory proteins of the coagulation mechanism plus homocysteine in a panel we call the HTRP (Hereditary Thrombosis Risk Panel). In July 2001, at the International

Hypercoagulation & Heparin
A Second Look

Patricia Kane, Ph.D.

It has been suggested that the use of heparin will address hypercoagulation. Recent data from JAMA[1] indicates that the use of low dose heparin may transform a 'benign fungal infection into a toxic shock-like reaction'. This research was presented at the 39th annual meeting of the Infectious Diseases Society of America in 2001 by Margaret K. Hostetter, M.D.[2, 3] of Yale University School of Medicine. Hostetter and colleagues found that Candida albicans can attach to host cells and form invasive hyphae which ultimately may create virulence of C. albicans. Low dose heparin utilized in hospitalized patients through the practice of heparin in intravascular catheters may transform the yeast into a life-threatening pathogen[1]. The use of heparin raises the cytokines TNF alpha[1] and IL-6[1] in addition to Phospholipase A2.[4, 5, 6]. Biotoxins which form neurotoxins, may create a state of hypercoagulation from the rise in TNF alpha. Consequently, the use of heparin may exacerbate the neurotoxic condition and hypercoagulation.

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Berg Interview *continued*

Society of Thrombosis and Hemostasis meeting in Paris, we presented data from a retrospective study of over 400 chronically ill patients, 83% had one or more demonstrable coagulation protein defects. Forty percent of the patients had a thrombophilia defect (decreased protein C, decreased protein S, decreased anti-thrombin, APC resistance / factor V Leiden positivity, or increased prothrombin / prothrombin gene mutation positivity). 39% of the patients have defects in the fibrinolytic system (hypofibrinolysis due to elevated lipoprotein (a) - Lp(a) and / or PAI1-plasminogen activator inhibitor-1. 21% of these patients had a defect in both the thrombophilia and hypofibrinolysis marker groups. This means that not only do they form fibrin easily, but also they are compromised in the ability to clean up the fibrin deposition.

Let's put this in plain English. When a pathogen(s) gains a foothold, especially in the endothelial cells in the blood vessels (as well as other cells), the bug(s) can be protected by the coagulation mechanism of fibrin deposition on top of the infected cells. Half of the patients form fibrin very fast, becoming fibrin(oid) deposition. Half of the patients have an inability to clean up the fibrin, and therefore continue to have oxygen and nutrient starvation of tissues for a long time. For example, if the fibrin deposition occurs in a muscle, it says "ouch," and you have a tender point as in Fibromyalgia. If it is in the placenta, the placenta is compromised by fibrin deposition and the baby aborts. As blood viscosity increases and blood flow is reduced throughout the body, the patient becomes hypo-this and hypo-that, such as hypothyroid, hypo-HPA axis, hypo-estrogen, etc. The use of low dose heparin restores blood flow throughout the body and hormones from the endocrine system tend to normalize. Thus, the blood flow issue becomes one of the most important issues of chronic illnesses. Unfortunately there is no easy test to measure blood flow, only the effects of blood flow.

If you consider the movie "Braveheart" (1000 AD) and you went to battle and were wounded, you probably would have bled to death unless you clotted fast. By clotting fast, you saved your own life and passed on this new trait to your children. This hypothesis may explain how these coagulation defects were genetically selected during the last 2000 years in Europe. Life expectancy back then was only 30-40 years. With our life expectancy now of 80+ years, these traits are no longer beneficial, but rather deleterious to our health. It was the Spanish, French, British, Germans, Italians, Scandinavians, etc. (Europeans) that colonized the Americas. This explains why most of the chronically ill patients are white people of European decent. Therefore we have a genetic basis in the coagulation system for chronic illnesses that is very straightforward.

The model of reduced blood flow from increased blood viscosity due to activation of coagulation accompanied by a coagulation protein defect gives a scientific basis for a contribution to the pathophysiology of chronic illness. It also gives a measurable or quantifiable, objective aspect to testing the blood of patients with these diseases. It is no longer "all in your head", but rather in your "blood." It's not rocket science, but a simple, logical explanation for what's going on in many chronically ill patients.

HEMEX Laboratories provides testing services and consultative interpretations to clinicians and physicians throughout the United States. For more information, technical reprints, and / or patient information, please see their website at www.hemex.com. ■

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In This Issue:

Hypercoagulation Linked to Chronic Fatigue, Fibromyalgia, MS, Infertility, & Chronic Illness

Potent Natural Anticoagulant Enzyme Derived From Traditional Japanese Food

"The literature about natto and nattokinase is very impressive. The first patient we asked to try it had a rapid and dramatic response. While this was likely an unusually good result, nattokinase appears to be a true therapeutic breakthrough."

Jonathan Wright, M.D.

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