

Focus

Allergy Research Group®

Allergy Research Group® Newsletter

November 2008

Nattokinase: Clinical Updates from Doctors Support its Safety and Efficacy

• Doctors Apply Nattokinase in Many Conditions

By dissolving branched fibrin—which coagulates prior to full clot formation—nattokinase proves uniquely helpful in many disorders.

Turn to page 2 for more on *Doctors Apply Nattokinase in Many Conditions*

• A Potent and Safe Thrombolytic: By Martin Milner, N.D.

Clotting is a key, often overlooked factor in chronic illness, and with nattokinase, we know how to reverse it. This is where the real treasure of this enzyme lies. Disorders such as heart disease, hypertension, fibromyalgia, chronic infection, inflammatory bowel disease, deep vein thrombosis, may respond to nattokinase.

Turn to page 2 for more on *A Potent and Safe Thrombolytic*

• Four Top Doctors Weigh In

Hear how Jonathan Wright, M.D., David Brownstein, N.D., Christopher Deatherage, N.D., and Stephen Hines, N.D. use this powerful, fibrinolytic enzyme

Turn to page 6 for more on *Four Top Doctors Weigh In*

The Guts and the Glory: Two Remarkable Nutraceuticals Support Gastrointestinal Health

• Zyactinase: An Enzyme for Constipation, Diarrhea, and Gut Health - Special Extract from Kiwi Fruit Contains Enzyme that Heals the Intestinal Tract

Zyactinase has a three-way mode of action that increases stool volume, increases gut motility, and serves as a prebiotic to improve gut microflora

Turn to page 8 for more on *Zyactinase: An Enzyme for Constipation*

• A Novel Probiotic and Prebiotic for Gut Health - Short Chain Fatty Acids in Propionic Bacteria Dramatically Enhance Colon Health

Propionic bacteria produce natural biological acids that protect the colon, improve bowel transit time, and selectively stimulate bifidus bacteria

Turn to page 10 for more on *A Novel Probiotic and Prebiotic for Gut Health*

In This Issue

Nattokinase: Clinical Updates from Doctors Support its Safety and Efficacy

- Doctors Apply Nattokinase in Many Conditions 2
- A Potent and Safe Thrombolytic: By Martin Milner, N.D. 2
- Four Top Doctors Weigh in . . 6

The Guts and the Glory: Two Remarkable Nutraceuticals Support Gastrointestinal Health

- Zyactinase: An Enzyme for Constipation, Diarrhea, and Gut Health - Special Extract from Kiwi Fruit Contains Enzyme that Heals the Intestinal Tract 8
- A Novel Probiotic and Prebiotic for Gut Health - Short Chain Fatty Acids in Propionic Bacteria Dramatically Enhance Colon Health 10

Allergy Research Group®

2300 North Loop Road, Alameda CA 94502

Phone: 800-545-9960/510-263-2000

Fax: 800-688-7426/510-263-2100

www.allergyresearchgroup.com

Nattokinase: Clinical Updates from Doctors Support its Safety and Efficacy

Doctors Apply Nattokinase in Many Conditions

Introduction: Six years ago in our special issue on nattokinase, Martin Milner, N.D., announced, "In all my years of research as a professor of cardiovascular and pulmonary medicine, nattokinase represents the most exciting new development in the prevention and treatment of cardiovascular related diseases." In this issue, Dr. Milner follows up with a detailed report on exactly how he uses nattokinase in his clinical practice. His experience with nearly 300 of his patients who have taken the enzyme leads him to conclude that: "I believe there is a low-grade chronic coagulation disorder that is very broad-based throughout the United States, as evidenced by the prevalence of cardiovascular disease. Clotting is a key factor in the evolution of chronic disease. With nattokinase, we know how to stop it. Nattokinase

helps keep blood optimally flowing more than any other single intervention that I use."

Back in 2002, we theorized that by dissolving branched fibrin—which coagulates prior to full clot formation—

nattokinase might prove uniquely helpful in a range of disorders in which hypercoagulation is involved. This includes atherosclerosis, infertility, high blood pressure, dysmenorrhea, fibromyalgia, deep vein thrombosis, varicose veins, hemorrhoids, and ischemic strokes. We also suggested it would prove helpful in chronic infections, where the body lays down fibrin in an attempt to seal off harmful pathogens. Finally, we concluded that nattokinase could be helpful in slowing many age-associated illnesses, since high fibrin levels create local pathology and ischemia, and block nutrient and oxygen delivery in microcirculation. Six years later, with nattokinase widely in use, firsthand clinical reports from doctors around the country support our hypotheses and the enzyme's impressive record of efficacy and safety in a wide range of disorders.

In this update we will report on:

- How to diagnose functional clotting problems before obvious clinical disease.
- Why chronic, insidious, low grade clotting can damage blood vessel walls, leading to many of the "diseases" of aging.
- A simple test that can be done in the office to determine whether a patient is clotting at a faster than optimal rate.
- How Coumadin and nattokinase differ.
- The conditions that nattokinase may help.
- Why the over-40 population may already suffer from chronic, subclinical hypercoagulation.

Nattokinase: A Potent and Safe Thrombolytic

By Martin Milner, N.D.

The enzyme nattokinase offers a completely natural means of helping prevent and dissolve blood clots. It closely resembles plasmin, our own natural clot-dissolver, and actually enhances our body's production of plasmin. Nattokinase cleaves fibrin (the protein that helps our body form the 'mesh' of a clot from a wound or

trauma). It is like our natural plant kingdom source of plasmin, and is the most potent fibrinolytic enzyme of nearly 200 foods studied for their clot-dissolving abilities. It can even outperform our own body: in one remarkable in-vitro study, nattokinase, urokinase and plasmin (all capable of dissolving clots) were placed on a plate

of fibrin. A clear halo showed degraded fibrin. The halo around nattokinase was over twice the size of the halo created by the other two enzymes, which our body manufactures. It also more potent than garlic, bromelain or ginseng.

I have now used nattokinase with around 300 patients. It is truly a

multidimensional supplement, useful in each of the following conditions:

- Arterial wall thrombi formation with atherosclerosis
- Atherosclerosis
- Coronary artery disease (CAD)—heart attack prevention
- Pulmonary embolism
- Atrial chamber thrombi present in chronic atrial fibrillation
- Thrombi in the eyes—known as vena Centralia retinae acresia
- Diabetes, which often leads to excess platelet aggregation
- Hypertension—a natto rich diet or nattokinase supplements have been shown to lower blood pressure. The microscopic trauma to a vessel wall under high pressure increases platelet aggregation and the need for blood thinning in the long term management of the prevention of CAD and strokes in the presence of hypertension.
- Peripheral vascular disease—arterial atherosclerosis or venous thrombosis. Nattokinase almost always improves spider veins and varicose veins. Hemorrhoids are improved as well.
- Senile dementia in which there is poor circulation and blood supply or cerebral thrombi formation
- Ischemic stroke—prevention
- Chronic migraine—where platelet aggregation releases vasoactive chemicals implicated in migraines
- Fibromyalgia, CFS and Lyme Disease—where chronic infection produces antibodies that cross-react with endothelial cells, leading to fibrin deposition
- Dysmenorrhea—where excessive clotting causes painful cramping
- Excessively fast clotting times due to platelet aggregation

Nattokinase and Cardiac Disease: A Profound Intervention

Cardiac disease is the single leading cause of death in America. Stroke is the third leading cause. In 2005, nearly 81 million Americans suffered from high blood pressure, coronary heart disease, stroke or heart failure. But functional clotting problems do steady, silent damage long before obvious disease shows itself. If we can reverse silent,

Nattokinase is truly a multidimensional supplement, and can play a key role in treating hypertension and hypercoagulation.

functional clotting problems, we can offer a profound healing tool to patients. This is where the real treasure of this enzyme lies, and allows us to treat cardiac disease in a way that puts our patients at the forefront of preventive medicine. In fact, by breaking down fibrin, increasing blood flow and thus tissue oxygen levels, we are lowering a

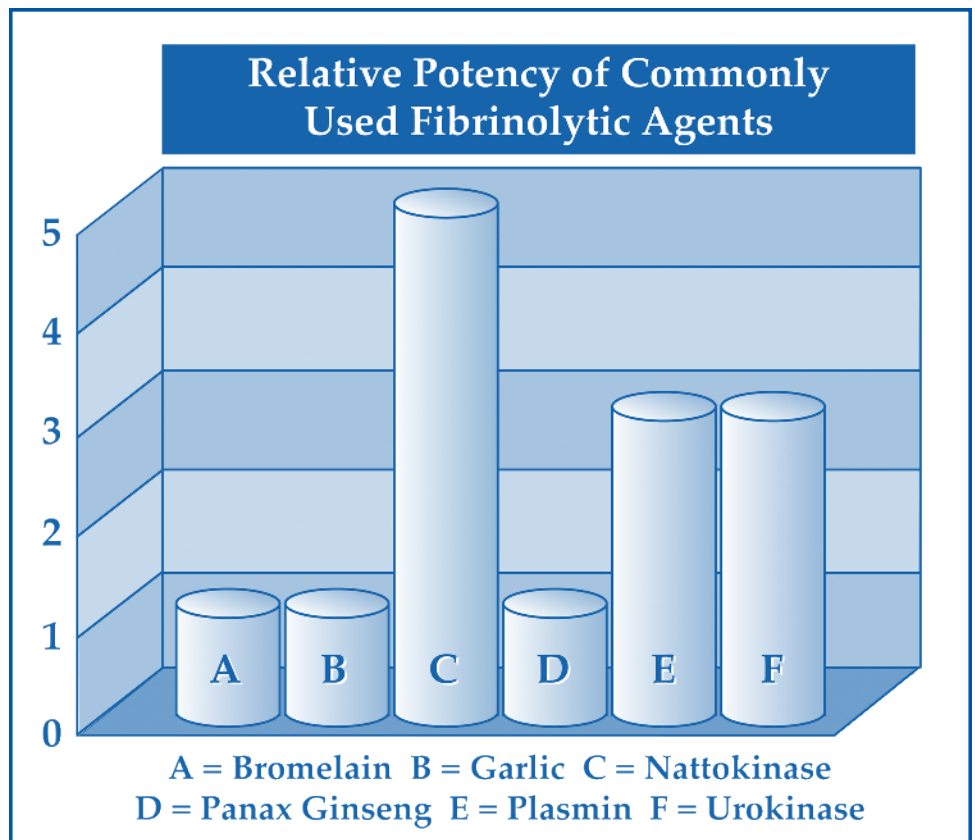
risk factor that is implicated in almost all chronic disease.

Atherosclerosis is a multidimensional and evolving disease process, one that begins with free radical attack on the lining of the blood vessels. In fact, atherosclerosis is much like wound healing gone awry: an area becomes inflamed and ‘wounded’, and the body brings in fibrin and platelet aggregates to repair the wound. Before pulmonary emboli, heart attacks or strokes occur,

patients accumulate small micro-thrombi that are still reversible. These thrombi develop and are maintained by the gradual accumulation of excessive fibrin and by the inability

of the body to break down the fibrin strands effectively. Inflamed plaques produce chemicals that slow down our innate clot-dissolving ability.

Micro-embolization is an often overlooked component of atherosclerosis. It is fibrin that is implicated in many heart attacks, since



**A = Bromelain B = Garlic C = Nattokinase
D = Panax Ginseng E = Plasmin F = Urokinase**

cardiac arrest usually occurs after a plaque's cap fractures, causing a blood clot to form over the fracture and block blood flow. Nattokinase is an ideal treatment, therefore, for heart attack patients, ischemic stroke patients, those at risk of pulmonary embolism or deep vein thrombosis—in short, any patient with a clotting problem.

Hypertension is another hallmark of atherosclerosis. Fifty million Americans suffer from hypertension. By the time hypertension manifests, the blood vessel wall is already damaged and thickened by platelet aggregation. Yet the mainstream treatment strategy is simply to lower blood pressure with medications, never considering why the hypertension is occurring in the first place or how to prevent the effects of hypertension from inducing further clotting.

Nattokinase can play a key role in treating hypertension, as well as preventing the long-term sequelae of damaged, inflamed blood vessel walls. Proof of nattokinase's efficacy in treating high blood pressure comes from a new, randomized, controlled trial published this September in *Hypertension*. Scientists at Yonsei University in Korea tested 86 individuals aged 20 to 80 whose blood pressure ranged from 130 to 159 mmHg. Each received either nattokinase at 2000 FU (fibrinolytic units) per capsule daily or a placebo. After eight weeks, those on nattokinase had significantly lower systolic and diastolic blood pressure. The researchers conclude, "These findings suggest that increased intake of nattokinase may play an important role in preventing and treating hypertension."

Why Nattokinase is Unique

Medical science has synthesized various compounds to help thin blood, from aspirin to warfarin, urokinase and streptokinase. Each has their role. Warfarin, for example, blocks factors in the Vitamin K clotting cascade. However, warfarin does not help a patient lower their platelet aggregation

or dissolve their fibrinogen or existing clots. A patient on warfarin is only treating one part of the clotting cascade and dietary Vitamin K toxicity has not been shown to be a significant etiology in cardiovascular disease. These patients with high fibrinogen and persistent platelet aggregation are still a walking time bomb. Nattokinase is unique in profoundly lowering fibrinogen levels and degrading branched fibrin. It has three different mechanisms of action. It lyses fibrin directly, changes prourokinase to urokinase, and increases tissue plasminogen activator, which increases our own plasmin. At the same time, nattokinase does not appear to actually destroy the fibrinogen molecule, as streptokinase and urokinase do. It is in a unique class of fibrinolytic agents.

Are We Suffering From A Widespread Chronic Coagulation Disorder?

Nattokinase lessens excessive coagulation and thus improves circulation, increasing oxygen to tissues. That is one reason disorders such as fibromyalgia, chronic fatigue syndrome, and chronic infections such as Lyme disease and inflammatory bowel disease may respond to nattokinase.

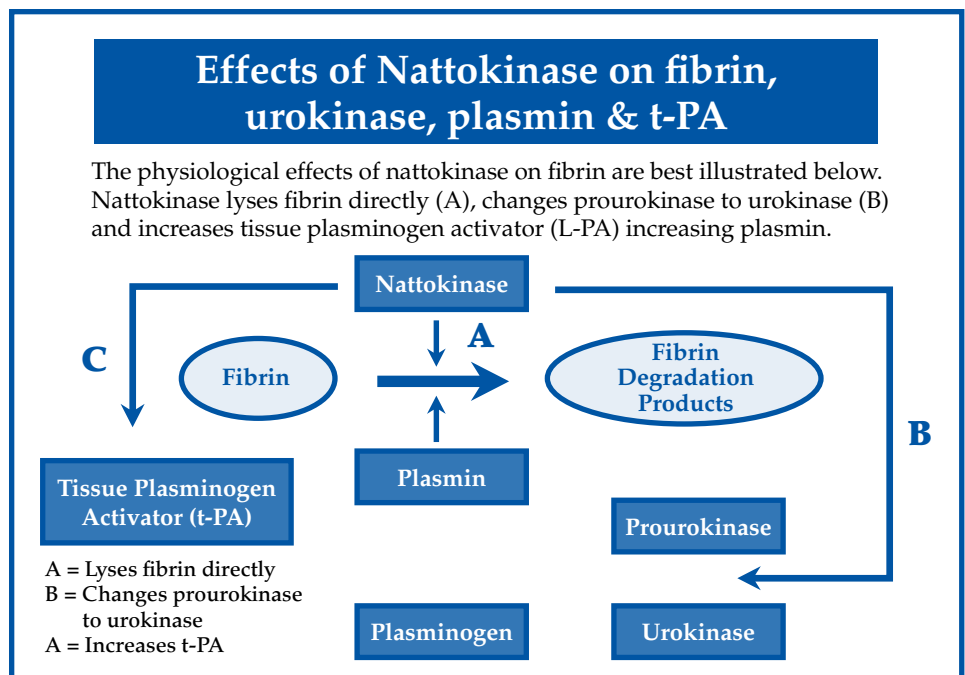
These conditions are in part triggered by pathogen-associated fibrin deposition that leads to tissue hypoxia.

In chronic infection, antibodies generated in response to pathogens can cross-react with endothelial cells. The pathogens themselves induce an antibody response that is damaging the endothelium and the capillary bed. In a milieu of chronic inflammation and infection, fibrin and soluble fibrin are deposited by the body in response to the "wound". This causes local ischemia and local tissue hypoxia.

In fact, taking these conditions as a model, we might describe a new syndrome called chronic coagulation disorder. Most of us over the age of forty probably suffer from this to some degree. Ensuring that our blood is flowing optimally and bringing healing oxygen to every cell is an important preventive measure.

A Few Remarkable Cases

In general, I consider a low dose one 100 milligram/2000 FU softgel capsule 2 or 3 times a day; a medium dose two capsules 2 or 3 times a day, and a high dose three to four capsules 2 or 3 times a day. Capsules are taken on an empty stomach.



DVT (deep vein thrombosis) Resolution with Nattokinase: This 83-years-young gentleman arrived at our clinic over 3 years ago, in early 2005, presenting with a large DVT confirmed on Duplex Doppler Ultrasound (1/10/05) involving his left calf and knee associated with ultrasound confirmation of DVT involving his left popliteal, posterior tibial and peroneal veins. On physical exam the left calf was 50 cm, left knee 37.5 cm and the right calf 37.5 cm, the right knee 34.5 cm in circumference with mild left calf erythema and 1+ pitting edema. He refused conventional medical intervention suggestions of Warfarin. We initiated treatment with Nattokinase 100 mg (2000 FU), initially given at 3 BID increased to 6 BID after one month, taken away from food. In order to enhance resolution while continuing Nattokinase we increased the patient's

consumption of flaxseed oil (patient is vegetarian and doesn't use fish oil) from 4 to 8 tablespoons twice daily and added Bromelain (3,200 BCU) 2 BID, away from food and away from Nattokinase. In order to further speed resolution after two months we added Ginkgo Biloba 300 mg twice daily. Fibrinogen and bleeding times were tracked to guide in the safe adding of these integrated therapeutics without

If we can reverse silent, functional clotting problems, we can offer a profound healing tool to our patients.

causing excessive blood thinning, bruising or other side effects. Repeat Doppler Ultrasound on 7/25/05, six months later, reported: "We compare with prior study done here 01/10/05. Today all vessels show normal lumina, normal flow, normal augmentation, no residual clots nor stenoses identified."

Migraines: I've seen migraines clear up using nattokinase, which leads me to speculate that subclinical clotting disorders may be stimulating the release of the vasoactive chemicals implicated in migraines. One woman suffered from fibromyalgia and chronic migraines. After two weeks of taking nattokinase, her migraines vanished. Another woman who'd suffered a pulmonary embolism also found her migraines cleared up taking nattokinase. Finally, a fifty-year-old female who'd had five deep vein thromboses leading to pulmonary embolism but no new occurrences since aggressive vein stripping, also had a long history of migraines two to three times weekly. She began taking two nattokinase twice a day and for thirty days there was not a single migraine. When she finally did get a migraine she only experienced nausea and visual changes, but no pain.

A Simple Test for Bleeding Times

So how do we test for excessive clotting? Platelet aggregation and excess fibrinogen start long before you can measure excess factors in the Vitamin K clotting cascade (factors that usually rise after an actual injury to the blood vessel). Vitamin K levels, prothrombin and thromboplastin times will not be abnormal with individuals who are not taking Warfarin unless they are taking very high doses of Vitamin K. And it is the rare patient who will show abnormally high levels of platelets on a complete blood count. Dark-field microscopy can be useful, but many physicians don't own such a machine. Platelet function assays are also useful yet are often normal unless the platelet abnormality is severe.

There is, however one test that has been performed reliably for years, and that is a simple, in-office test for bleeding/clotting times. It is an excellent strategy for assessing optimal blood flow in patients. The duration of bleeding from a standard skin incision is determined while maintaining constant increased venous pressure. Bleeding time measures the overall hemostatic role of platelets. A shortened bleeding time (rapid clotting) is due to excessive platelets and/or aggregation.

You will need a blood pressure cuff, a standard "Surgicutt" lancet for a controlled incision, and clotting paper to touch gently to the side of the drop of blood every 30 seconds. This test will reveal a patient's actual bleeding time. A normal reference range is about two to eight minutes, although some laboratories allow ten minutes. I see a lot of patients at 2-3 minutes, but personally, I feel 4-6 minutes is optimal normal finding and targets may need to be as high as 8-12 minutes for chronic anticoagulant therapy. I've seen patients on a whole array of blood-thinning nutraceuticals such as fish oil, ginkgo and garlic, who still have bleeding times of only 3 minutes. So I never assume someone is protected. I test them to verify they are at the optimal platelet aggregating target.

When I looked at the research I found that platelet aggregation induces serotonin, histamine, epinephrine and norepinephrine—all powerful vasoactive substances that may destabilize the vascular bed and perhaps lead to migraines. I now believe every migraine patient should be tested for bleeding/clotting times.

Intermittent claudication: Nattokinase proved to be an excellent intervention for a woman with advanced peripheral vascular disease and hypertension. She had already undergone a bypass operation in 1999 and subsequently developed severe intermittent claudication with bilateral calf and thigh pain. The pain woke her frequently at night and disturbed her sleep for years. In spite of two decades of use of natural medicine, high doses of fish oil, and chelation once a month for five years and then once a week for another year, she had no improvement in the pain. In July of 2002 she began taking two capsules of nattokinase on an empty stomach and within a few weeks her leg pain began to abate and she was able to sleep through the

How Four Top Doctors Are Using Nattokinase

— Jonathan Wright, M.D.: Nattokinase: An Effective Answer to Hypercoagulation —

I've been using nattokinase since it first became available here and it is very effective. I think of this enzyme like the guards at Buckingham Palace. They stand there stock still—you've seen those famous photographs where you can tickle a guard's nose with a feather and he won't move. But if you try to enter Buckingham Palace, the guards spring into action. Well, that's nattokinase. It stands there stock still and the one thing it responds to is a clot, or specifically fibrin. When fibrin starts to form—bingo, nattokinase goes into action.

Let's go for a moment to the idea of Coumadin. It thins out the blood by poisoning the part of the coagulation system that's dependent on Vitamin K. Now that's certainly one way of approaching clots. Another way is fish oil. Studies on Eskimos found they have half the risk of atherosclerosis of anyone anywhere in the world. However, what doesn't get talked about is the fact that they have a far greater risk of stroke when a blood vessel is weak and bursts and can't clot at all. Fish oil is basically doing a lube job on the bloodstream. My approach is to recommend two tablespoons of fish oil daily, which is not going to stop you from clotting. Then add in nattokinase to dissolve fibrin. This will offer an effective and safe treatment for coagulation disorders.

I've seen the remarkable efficacy of nattokinase in one of the young physicians in our clinic. In her late twenties she suffered from recurrent mesenteric arteriosclerosis. The artery that branches off into the intestines kept developing thrombi that would block blood flow, causing excruciating intestinal pain. Every few weeks she'd be

home for a few days with terrible cramps. Her doctors wanted to put her on Coumadin but she is a naturopath and refused. She also was allergic to fish, so could not take fish oils. We put her on nattokinase every 8 hours. I ask people to use it before they go to bed, when they get up in the morning, and once in the middle of the day, because the research shows that the effects vanish after about eight hours. This young woman has not had a single problem since she began the nattokinase.

Another dramatic case comes from a woman who wrote to me in response to my newsletter article on nattokinase. She wrote that she had a chronic deep vein thrombosis that blocked flow from her ankle to her groin. She had been lucky thus far, because the clot had not thrown off microclots to her heart or lungs. She was told she needed surgery, that Coumadin was not enough. She wrote me that she began taking a double dose of nattokinase every eight hours, on her own, and within four months the clot had been slowly eaten away. Tests showed it had simply dissolved.

So, for anyone who has just had a heart attack and is trying to prevent a recurrence, or just had an ischemic stroke and doesn't want to suffer another, or for any indication where Coumadin is recommended, run as fast as you can to your nearest natural medicine doctor, someone who really knows what they're doing, and ask them about fish oil and nattokinase. If we combine the two our odds are exceptionally high that we'll have an effective answer to hypercoagulation without putting a person at risk by poisoning their Vitamin K cascade.

— David Brownstein, N.D.: Nattokinase and Bone Pain —

At our clinic we have fabulous results with nattokinase. We use it for hypercoagulation states and clotting disorders. One gentleman been diagnosed with hemochromatosis, an iron overload disorder that requires therapeutic phlebotomies. We had a very difficult time performing those phlebotomies because his blood was so thick and it was a very painful experience for him. With just ten days of nattokinase he was able to undergo the therapy without a problem.

An older woman with bone pain said her pain vanished when she took nattokinase. Many older women complain of bone pain, but you don't want to put them on Coumadin and upset their Vitamin K cascade since that helps form a protein in bone. Nattokinase may do the trick. I also am treating a lady right now who was prescribed Coumadin for atrial fibrillation, and she just could not tolerate it. It was her choice to try nattokinase instead and she has done fabulously with it.

— Christopher Deatherage, N.D.: Nattokinase and Dysmenorrhea —

I've been practicing for 23 years in the Ozark mountains and my practice focuses on both naturopathic and functional medicine. We look for underlying causes for illnesses and one common underlying causes is hypercoagulation. One condition for which we've

used nattokinase where it's proved nearly miraculous is dysmenorrhea. A lot of women who come to us suffering from painful menstrual cycles are helped with a standard naturopathic protocol of hydrotherapy, lifestyle and nutrition changes and botanicals. But about

20% are not helped and they are miserable every month. The fact is that the pain is caused by excessive clotting and sending clots through the cervix, and nattokinase relieves the pain. I don't know of any other doctor in the country using nattokinase for dysmenorrhea. Most interesting of all was one out-of-state patient of mine who had a complete hysterectomy for endometriosis and still had monthly cycles of pain. This pain cleared up completely on nattokinase.

Nattokinase is also very effective in fibromyalgia, although I'm not sure we understand the exact mechanism. Most of my fibromyalgia patients improve

remarkably on nattokinase, with a standard dose of two capsules twice a day. Nattokinase is also beneficial in atrial fibrillation, because of the danger of throwing a clot. I treat a 77-year-old pathologist and physician who has atrial fibrillation and is doing very well. She is walking every day. One of the supplements that really made a difference for her was nattokinase. We work with a cardiologist and always bring him in on such cases.

In sum, I think nattokinase is a wonderful supplement. It might just be possible that this should be a standard supplement for patients over forty.

— Stephen Hines, N.D.: Nattokinase and Lyme Disease —

Lyme Disease is my specialty. I am a lyme patient myself and I use myself as a test subject for any therapy I use on my patients. When you have a chronic infection that gives rise to fibromyalgia and chronic fatigue symptoms, you will deposit excess fibrin in your tissues, and that will trigger a secondary immune response. Your body deposits fibrin so that organisms are inhibited from being very mobile. That is both good and bad. They're not

mobile, so they can't do as much damage, but you also can't get antibiotics or other medications to them as easily. Ultimately, in order to treat the infection, we want to get deep into the tissues and this is where nattokinase has a powerful role. I start my patients on nattokinase and build them up slowly, and once they have reached a peak level and the pathogens are exposed and vulnerable, I add in the antibacterial, antifungal, or antiviral medications.

night for the first time in years. Over a six month period she reported no side effects and only two episodes of nighttime awakening. Considering her history of hypertension and severe peripheral vascular disease I believe that she also had micro-thrombi in her lungs and was at risk for emboli in her heart. This is a highly under-assessed risk conventionally, and I am convinced the nattokinase is protecting her from a dangerous clotting episode.

Fibromyalgia: A patient came to me with a longstanding history of chronic fatigue and fibromyalgia, hypothyroidism, chronic migraines, GERD, colitis, leg cramps, mild osteoporosis, degenerative disk disease, osteoarthritis of one knee, varicose veins, obesity and hypertension. She was a classic example of a chronic patient with multiple health challenges who had

been taking many supplements for many years. She began with two capsules of nattokinase twice a day and then increased to three capsules twice a day. Her energy improved and there was complete resolution of her headaches. Interestingly, her varicose veins also improved.

COPD and Pulmonary Hypertension: A forty-nine year old patient with pulmonary hypertension visible on an echocardiogram as enlargement of the right pulmonary ventricle of the heart and COPD with 30% reduction in pulmonary function was very short of breath. I wondered how much of her problem was due to micro-thrombi in the pulmonary vasculature, and how much was permanent damage due to COPD. After 2-3 days on nattokinase she reported that breathing was easier and she was able to walk around the block and go grocery shopping. Before

then she could not walk at all without shortness of breath. For a patient so disabled, such improvement meant a whole new level of freedom in her life.

Clotting is a Key Factor in Chronic Illness

To make a long story short, clotting is a key, often overlooked factor in chronic illness, and with nattokinase, we know how to reverse it. We can safely and accurately monitor the dose of nattokinase with target fibrinogen levels at 275-325 and bleeding times using a Surgicutt lancet targeted to 7-12 minutes.

The management of chronic coagulation is a new huge horizon in the prevention and treatment of cardiovascular and peripheral vascular disease and has wide implications for the effective treatment of many other chronic diseases as well.

Coming in the next issue of *Focus*:

How nattokinase may uniquely inhibit PAI-1 (plasminogen activator inhibitor), which has recently been identified by the *New England Journal of Medicine* and by researchers at Vanderbilt University as a key factor in ischemic heart disease.

The Guts and the Glory

Two Remarkable Nutraceuticals Support Gastrointestinal Health

Two new developments in gastrointestinal nutrition may change the landscape of gut health and immune function. In this issue we feature two remarkable new nutraceuticals: Zyactinase, a uniquely processed enzyme from kiwi fruit that has a tonic effect on the entire gut, stimulates healthy lactobacilli and other lactic-acid flora, speeds bowel transit time and increases gut motility. We also look at the scientific research on an impressive, new probiotic that functions as a unique prebiotic, selectively stimulating bifidobacteria, the essential, health-promoting flora in our colon.

An astounding 100 trillion microorganisms thrive and happily beget themselves in our guts. They constitute

a microbiome, a kind of super-organism made of microbial life, according to Jeffrey Gordon, M.D., the Dr. Robert J. Glaser Distinguished University Professor at Washington University in St. Louis, and one of the architects of the National Institutes of Health's Human Microbiome Project. In fact, descendants of the most ancient single-celled organism, the "mother" organism, archaea, can be found in our digestive tract. Fossils of archaea date back to about 3.5 billion years ago. Scientists first isolated archaea from the human intestine in 1982. Our microbiota are evidence not only of evolution's awe-inspiring creations, but of how closely allied we are with the microbial world.

Research already shows that micro-

biota choreograph multiple important functions, such as producing essential vitamins, metabolizing toxins, fermenting food in our gut, manipulating our gene activity, influencing the rate at which our gut lining renews itself, and helping regulate everything from blood pressure to obesity. Our microbiota are potent regulators of human health, and our "healthy" native flora help eliminate potential pathogens, and modulate innate and adaptive immune defense mechanisms. Microbiota may one day form the basis of a whole new pharmacopeia. The dawn of that day has already begun, as evidenced in the two new nutraceuticals that together can influence the entire digestive tract in a targeted, powerful way.

Zyactinase: An Enzyme for Constipation, Diarrhea, and Gut Health

Special Extract From Kiwi Fruit Contains Enzyme That Heals the Intestinal Tract

The most famous fruit in beautiful New Zealand—the kiwi, which was actually carried from China to New Zealand by a missionary and underwent an extensive breeding program to become the plump confection it is today—might not automatically bring to mind phrases about your feces like "snake or sausage like...loose, massive with rough edge, slurry-like... separate hard group, like stone..." But it turns out that an enzyme complex in kiwi fruit, when isolated and enhanced

through a special process, has a profound yet gentle normalizing effect on gut troubles, from IBS to constipation, diarrhea, impaction, and even food poisoning. It also shows promise in lowering cholesterol.

Zyactinase, a cysteine/serine protease enzyme complex from kiwi fruit, contains plant enzymes, polyphenols, dietary fiber, carbohydrates, sugars and oligosaccharides. "Kiwi fruit is extremely interesting," says cell biologist

Iona Weir, PhD. "My background is programmed cell death in plants. Kiwi fruit can actually initiate programmed cell death and completely recover from it. Once a human cell has committed to dying, it will die. But you can put kiwi fruit through a drought or other significant stress, and it will lock itself down, almost die, and then restore itself back to normal health. The enzyme that triggers this programmed cell death is also involved in cellular repair of the plant. Thus there is something quite unique

about this fruit.” In fact, notes Weir, kiwi fruit (*Actinidia deliciosa*) has long been known in traditional Chinese medicine for its ability to prevent and relieve constipation.

According to research Zyactinase has a three-way mode of action:

1. the cysteine/serine protease complex increases gut motility
2. the sugars and oligosaccharides in the extract serve as a prebiotic to improve gut microflora
3. the insoluble fiber in the extract helps increase stool volume

Zyactinase was tested on 400 individuals in 2007. Researchers also carried out two animal trials and two human clinical trials, and concluded that Zyactinase:

- Significantly improves constipation
- Is safe for human consumption
- Has dose-response correlation
- Has no negative side effects, including diarrhea, cramps, or damage to gut mucosa
- Has a beneficial effect in a follow-up period in which Zyactinase is no longer being taken
- Takes only 24 hours to improve tenesmus (painful, ineffectual bowel urgency), flatulence and abdominal pain; takes one week to increase gut motility; and two weeks to establish a significant prebiotic effect in humans
- Stimulates peristaltic motility

Zyactinase is Highly Effective in Treating Constipation

Two human clinical trials show that Zyactinase is a safe and effective treatment for constipation. In one double-blind placebo trial of 134 individuals with constipation, from the Chinese Center for Disease Control at Tianjing Centre Hospital, Zyactinase normalized bowel function without any side effects at all.

“Normal healthy subjects who had recently...developed constipation defined as no more than three bowel movements per week” were studied. Half received Zyactinase capsules, and half received a placebo. The study began with a two week washout period in which no supplements or medicines for constipation were taken. For the next two week treatment phase, each individual took four capsules a day of either placebo or Zyactinase. For the final two weeks individuals stopped

Even at very high doses there was no unpleasant laxative effect: stools were soft but firm. The combination of fiber, oligosaccharides and the enzyme complex has a unique protective effect.

taking any supplements or medicines for constipation.

The intrepid scientists scored both “defecation condition” and “fecal characteristics” based on the Bristol Stool Chart system. Tenesmus and discomfort, pain, or anal burning sensations were scored. So was the appearance of the stool, which was rated from a healthy smooth, soft, sausage like appearance, to slurry-like and loose, to hard like stone and difficult to pass.

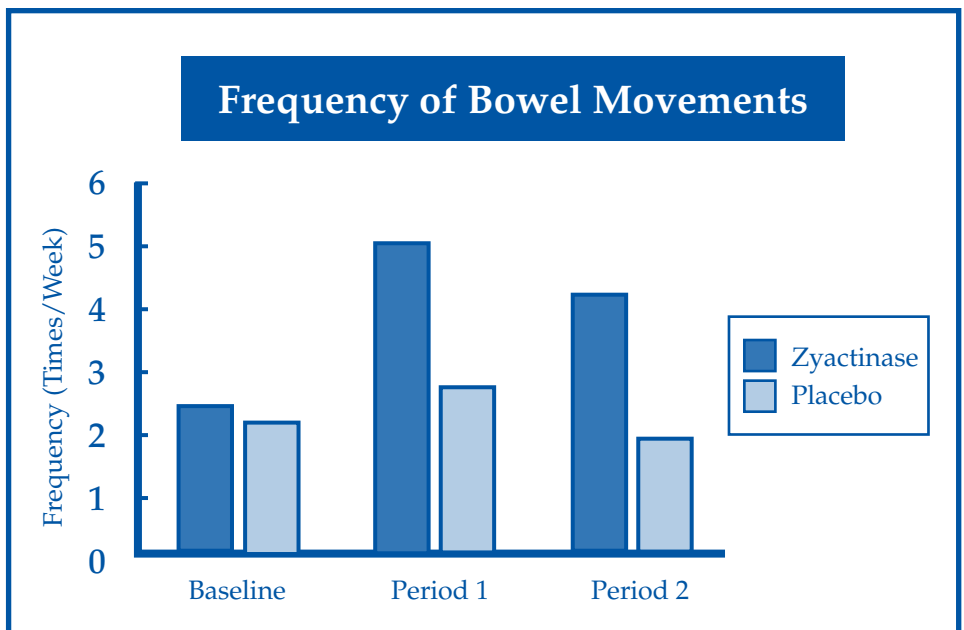
Results showed that the group taking

Zyactinase had more frequent bowel movements during and after the trial—both when compared to their pre-trial frequency, and when compared to the placebo group. The most significant increase occurred in the last two-week period, after supplementation, suggesting that the enzyme had actually rebalanced gut flora. The researchers conclude that, “the prebiotic effect takes time to build up in the system to relieve constipation.” In addition, the trial group had a statistically significant decrease in serum total cholesterol, while all other bloodwork stayed in normal range.

No negative side effects—no diarrhea, abdominal pain, discomfort, bloating, flatulence, or foul smelling feces—were observed in any of the individuals, either by themselves or by the doctors who examined them. In fact, IBS symptoms of tenesmus, flatulence and abdominal pain improved within the first 24 hours of consumption.

In a second clinical trial at Kaixian Traditional Chinese Medicine Hospital, 58 individuals were studied. Thirty were in the placebo group and 28 in the treatment group. All, like the first group, were healthy but had recently developed constipation, defined as no more than 3 bowel movements per

week.



week. A higher dose of six capsules per day (two capsules three times a day before meals) was prescribed. There was a one week washout period during which nobody used any supplement or medicine for the treatment of constipation, a one week treatment period, and a third week follow-up period when the individuals took no supplement or medicine of any kind for constipation.

In this study, a fecal score of 0 is the ideal, and consuming six capsules a day returned individuals to “near normal feces within the seven day feeding period.” The fecal score was 1.9, and remained very low in the follow-up period as well. In addition, near normal sensation (in terms of tenesmus or discomfort) was achieved by those in the treatment group during both the treatment and follow-up period. Finally, there was no diarrhea, which can often be the case with high doses of a motility stimulant. In summary of the two studies, the researchers conclude, “Although significance was achieved at both 4 and 6 capsules per day, there was definitely a stronger effect at 6 capsules.” Once again, there were no negative side effects; while there was a significant improvement in tenesmus, flatulence and abdominal pain in the first 24 hours, and increased bowel movements and softer consistency not only during the trial, but for the seven day post-treatment phase.

These results in humans tally precisely with animal studies, according to lead researcher Iona Weir, PhD. “The key finding of both the animal and human research is the strong correlation in dose response in the efficacy of Zyactinase,” she says. In animal studies, the effective human equivalent dose for severe constipation—initiated by a chemical called diphenoxylate, which inhibits peristalsis—was between four and eight capsules a day.

Zyactinase appears very safe: acute toxicity studies in animals show that Zyactinase is nontoxic at 500 times the normal daily dose, and in vitro tests of cellular toxicity on human cell lines found no toxicity. The enzyme was not cytotoxic. In other safety studies, eighty rats were divided into four groups: a control group and three separate dose groups, with 20 animals in each group. Dosages were set at the equivalent of 25, 50 and 100 times that of the recommended dose for humans. Rats were fed the extract by stomach tube. All of the animals’ activities, bodily functions and growth were normal, with the added benefit of thickening and glossing of the skin and hair. Weight and food consumption were the same for all the groups. On a separate test of mutagenic activity, the classic Ames test, Zyactinase had no mutagenic activity.

Zyactinase works in three ways to heal the gut

Existing treatments for constipation stimulate gut motility, bulk the stool, or increase the number of beneficial flora. Zyactinase has all three mechanisms of action, and is gentle as well. Even at very high doses there was no unpleasant laxative effect: stools were soft but firm. The combination of fiber, oligosaccharides and the enzyme complex has a unique protective effect.

When healthy human flora such as *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, and others were incubated with Zyactinase extract in an isomalt broth medium, the extract promoted the growth of each strain of beneficial flora, significantly more so than the isomalt medium alone.

In addition, the enzyme extract inhibited common food-borne pathogens such as *E. coli*, salmonella and staphylococcus.

When cells in culture were treated with the extract, Zyactinase actually stimulated renewal growth. Overall, Zyactinase is far more than a laxative or an antidiarrheal agent. It is a digestive aid that promotes long term intestinal health.

A Novel Probiotic and Prebiotic for Gut Health

Short Chain Fatty Acids in Propionic Bacteria Dramatically Enhance Colon Health

A **unique, new probiotic** that simultaneously functions as a prebiotic may be highly effective in enhancing colon health, and improving bowel function and constipation. *Propionibacterium freudenreichii* is a natural probiotic that has been used for centuries as a starter culture to make Swiss and Emmentaler cheeses. Propionic bacteria

are potent promoters of gut health: they produce natural biological acids and short-chain fatty acids that protect the colon, improve constipation and bowel transit time and, according to the latest research, may reduce the risk of colon cancer. They have been proven to increase bowel motility and improve constipation in healthy adults. At the same

time, these remarkable bacteria serve as a powerful prebiotic: bile-resistant strains of the bacteria can flourish in the lower gut and selectively stimulate bifidus bacteria, the dominant, healthy flora in our colon.

By stimulating our own native “good” flora, propionic bacteria bypass the

concern that a non-native strain might not “stick” or be well adapted to our body. For each of us has a gut ecology that is as unique as our own fingerprint, one fine-tuned over the years by genes, environment, microbes in food, diet, and especially our early source of milk (breast milk or formula). Propionic bacteria are an excellent complement to the health-promoting effects of widely used lactic acid bacteria such as acidophilus.

A New Probiotic Approach

We can shift our native flora by changing our diet, by supplementing with live probiotics, and by supplementing with prebiotics that stimulate the growth of healthy flora. Propionic bacteria are unique, food-grade probiotic organisms that are also highly effective prebiotics for bifidus bacteria. They are antimutagenic, produce vitamins, modify the composition and metabolic activity of gut microflora as well as the immune system, and produce bacteriocins—toxins that inhibit the growth of other bacteria. All this confers powerful health benefits, especially from bile and acid-resistant strains such as *Propionibacterium freudenreichii* (PF), which can survive the perilous journey to the colon. When eighteen individuals were given oral propionibacteria as a prebiotic daily for 14 days, the amounts of the prebiotic as well as bifidobacteria increased significantly in stool samples, as measured at 7, 14, and 21 days. By 28 days, however, levels had returned to baseline. In other research, seven healthy volunteers ingested propionic bacteria at low doses ranging from the equivalent of 10 grams of Swiss cheese to the equivalent of 100 grams of Swiss cheese. The bacteria survived the entire digestive tract and were detectable in significant numbers in feces. Just as important, short chain fatty acids (SCFA) increased. The SCFA butyrate has been studied for its ability to kill colorectal cancer cells; research now suggests that SCFA stimulated by PF, specifically propionate and acetate, probably serve the same role.

New research shows that PF probably

stimulates bifidus by producing a bifidogenic growth stimulator (BFG), specifically an acid called DHNA (1,4-dihydroxy-2-naphthoic acid). DHNA stimulates bifidus even at a very low concentration, and inhibits pathogenic bacteria in vitro. Other research has shown that DHNA is heat stable and resists proteolytic enzymes. Therefore it can reach the large intestine while retaining its activity. In addition, the short-chain fatty acid propionate inhibits gram-negative anaerobes in the intestine.

Propionibacterium freudenreichii Normalizes Bowel Function

PF has been proven to enhance gut motility and increase healthy flora in healthy women, according to a randomized, double-blind crossover study in Japan. PF was given in tablet form to 41 women, and the women were as-

“80% of the volunteers with diarrhea, and 79% of the volunteers with constipation said they would continue taking *Propionibacterium freudenreichii*.”

signed to two groups based on stool frequency (less than four times a week, or more often than four times a week). The experimental period consisted of four two-week periods. The first two weeks was a control period, and during the second two weeks, the women took tablets containing PF culture or a placebo after a meal. The women were asked to consume no other probiotics or prebiotics. They kept a record of stool frequency, and stool samples were collected between days 12 and 14 of each experimental period.

Bifidus bacteria were significantly increased in the stool of women taking PF. Putrefactive products, including fecal indole and skatole, was significantly lowered by the tablets. “Fecal indolic and phenolic compounds are associated with a variety of disease states in humans and animals,” write the researchers. The women who began the experiment with less than 4 bowel movements weekly had significantly

greater stool quantity and frequency when taking PF. The women with normal bowel frequency saw no change. PF, therefore, “increases the number of defecations of constipated volunteers.”

In another eight week, open-ended unpublished study, 30 volunteers who suffered from either constipation or diarrhea took PF. The volunteers were seen before the study began, at four weeks and at eight weeks. The volunteers complained of at least one of the following problems: distension, unpleasant odor, gas, or irregular stool frequency. The slow-transit “constipation” group took two capsules of PF in the morning half an hour before breakfast. The fast-transit “diarrhea” group took two capsules in the morning half an hour before breakfast, and two more capsules in the evening, half an hour before dinner. Volunteers kept a daily self-report based on questions evaluating quality of life and digestion.

At the end of eight weeks, both the diarrhea and constipation group had significant improvement in the ease of “transit”, in normalization of stool frequency, stool consistency and volume. For those with diarrhea, stool vol-

ume decreased, and for those with constipation, stool volume increased. Gas, odor and abdominal discomfort improved. By the end of the study, 80% of the volunteers with diarrhea, and 79% of the volunteers with constipation said they would continue taking PF.

PF can help resolve colitis, according to several animal studies. In one 2005 study, milk whey cultured with PF was given to rats suffering from colitis induced by injection of a powerful acid. Milk whey cultured with PF was given daily, twice a day, for nine days. Milk whey cultured with PF “significantly accelerated the healing of the colitis in a dose-dependent manner...to clarify the active substance, the effects of propionic acid and acetic acid contained in milk whey culture was tested.” Sodium propionate was discovered to be the healing acid, and the researchers concluded that, “Milk whey culture may become a useful probiotic for the

therapy of inflammatory bowel disease, and propionic acid may be one of the active substances."

In a second 2006 study from the journal *Gut*, DHNA (the active bifidus-stimulating acid in PF), was given to mice who were suffering from colitis induced by seven days of injection of dextran sodium sulphate (DSS). DHNA or a "control" substance was then given in drinking water for seven more days. Damage to the mucosa of the rats was scored, and measures of proinflammatory cytokines (IL-6 and TNF) were measured. Bacteria flora and concentrations of short chain acids were also measured. The researchers found that DHNA not only improved the survival of the rats, it significantly reduced inflammatory cytokines and mucosal damage. Healthy flora was restored, and butyrate concentration was restored as well.

"There was a significant difference between survival rates of the two groups", the researchers note. "DHNA was equally effective for both prevention and therapy of DSS-induced colitis...It not only attenuates the development of colonic inflammation but also has an inhibitory effect on established inflammation...partly through a decrease in...levels of proinflammatory cytokines. Our findings demonstrate for the first time that oral administration of DHNA attenuated colonic inflammation not only in relation to the traditional functions of prebiotics, such as balancing bacterial flora and increasing short chain fatty acids (SCFAs), but also by suppression of lymphocyte infiltration through suppression of proinflammatory cytokines and adhesion molecules. The results of the present study suggest that DHNA is useful for preventing and treating human IBD."

May Help Reduce Risk of Colon Cancer

What other health benefits might PF confer? Much anecdotal and scientific evidence suggests that health-promoting lactic acid bacteria may reduce the risk of colon cancer. A 2007 *in vitro* study on PF (published in the journal *Apoptosis*) found that the short-chain fatty acids in PF, acetate and propi-

onate, kill colorectal adenocarcinoma cells *in vitro*. This study found that extracellular pH mattered: at a pH range of 6.0-7.5, PF triggered cell death through apoptosis (or disintegration of cell membranes), in a process that could take as long as 96 hours. However, at a more acid pH of 5.5, the killing was far more rapid and "drastic", occurring in less than 24 hours, and characterized by "sudden mitochondrial depolarization, inner membrane permeabilization, drastic depletion in ATP levels and ROS accumulation, suggesting death by necrosis."

Similar results were found in a 2002 study in the journal *Cell Death and Differentiation*, where PF killed cancer cells "via the metabolic production of two short chain fatty acids (SCFA), propionate and acetate...our results extend the hypothesis that SCFA might have a prophylactic action on colon cancer...and could play a role in digestive cancer prevention."

The Beauty of Bifidus

Though *acidophilus lactobacillus* is well-known and well-studied, bifidobacteria actually outnumber lactobacillus strains by about 1000:1 in the human gut. That is an astounding number. The five common strains of Bifidobacteria are *B. infantis*, *B. adolescentis*, *B. bifidum*, *B. longum*, and *B. breve*. Human milk favors the growth of a "bi-

fidus flora" in the newborn, which is thought to activate the immune system and defend from pathogens. It may also normalize weight: a study of newborns found that those who were normal-weight seven years later had more bifidobacterium in their guts as babies; while those who were overweight by age seven had more *Staphylococcus aureus* in their guts as babies.

Bifidus protects against colonization with *E. coli*, rotavirus, clostridium, bacteroides, and enterobacteria. In a Brazilian study, mice treated with bifidus milk for ten days were protected when they were "challenged" with pathogenic bacteria such as salmonella. Bifidus may also have other wide-ranging health benefits. In one 2003 study, taking bifidus bacteria slowed the progression of renal failure in patients with a creatinine level more than 4.0 mg/dl. The researchers, from Jichi Medical School in Japan, speculated that lowering the level of intestinal putrefactive products helped protect the kidneys. And in a study from India, bifidus yogurt was found to reduce LDL cholesterol.

Together probiotics and prebiotics exert a synergistic impact on gut health. *Propionibacterium freudenreichii*, serving as both a probiotic and a prebiotic, may offer profound benefits to the entire digestive tract.

Heartburn and Indigestion Solution is a new electronic booklet in which you can learn simple and effective steps to heal heartburn and indigestion.

The signs and symptoms of Acid Reflux (GERD): Relief is not just about acid, but about the proper movement of food and fluid through the gastrointestinal tract.

In *The Heartburn and Indigestion Solution*, you can learn the program Dr. Galland has developed for addressing acid-reflux and indigestion naturally.

To get the natural secrets for fixing acid reflux and heartburn go to:
<http://fatresistancediet.com/alternative-medicine/gerd/>

About Dr. Galland

Leo Galland, M.D. is a board-certified internist who has been repeatedly chosen as one of America's Top Doctors and one of the Best Doctors in New York by *New York Magazine*. Dr. Galland is the winner of the Linus Pauling Award and the author of highly acclaimed books including *The Fat Resistance Diet* and *Power Healing, Use the New Integrated Medicine to Cure Yourself*. Dr. Galland is the Director of the Foundation for Integrated Medicine.

Focus on Allergy Research Group®

Editor-in-Chief: Stephen A. Levine, Ph.D.

Executive Editor: Jill Neimark

Medical Editor: Jeffrey L. Anderson, M.D.

Assistant Editors: Daniel Milosevich, CN, Diane Raile, CNC

Graphic Design & Layout: Christian Northcott

FOCUS publishes emerging nutritional science and scientific theories that should not be construed to be conclusive scientific proof of any specific cause, effect, or relationship. The publication is for the educational use of healthcare practitioners and physicians. The articles in the publication are the independent scientific views and theories of the authors. FOCUS takes no position on the views and theories expressed but offers them for candid inquiry and debate. The articles are not intended for use in support of the sale of any commercial product and should not be construed as indicative of the use or efficacy of any commercial product. Emerging science and scientific theories do not constitute scientific proof of any specific cause, effect, or relationship. Copyright © 2008. Allergy Research Group®. Special permission is required to reproduce by any manner, in whole or in part, the materials herein contained.