

New Enzyme Complex Isolated From Earthworms is Potent Fibrinolytic

Lumbrokinase has Anti-Platelet, Anti-Thrombotic Activity

By Edwin Cooper, Ph.D., Sc.D.

The earthworm's antioxidant, immune-boosting, and clot dissolving "medicine chest" is as powerful as that of any plant and even many pharmaceuticals. Lumbrokinase may be effective in the treatment and prevention of ischemic heart disease, myocardial infarction, thrombosis, and pulmonary embolisms.

Turn to page 2 for more on New Enzyme Complex is Potent Fibrinolytic.

Cancer and Hypercoagulation: How One Doctor Keeps Fibrinogen Levels Low in his Cancer Patients

Q & A with Naturopath Physician James Belanger

A whole array of studies links excess fibrinogen and hypercoagulation with the spread of cancer. Lowering fibrinogen is very important in treating a cancer patient.

Turn to page 6 for more on Cancer, Hypercoagulation and Fibrinogen Levels.

Dissolve Biofilms with Fibrinolytic Enzymes: One Nutritionist's Novel Approach to Autism Spectrum Disorders

Biofilms are a huge missing piece in Autism, Lupus, Lyme Disease, Multiple Sclerosis and any autoimmune-type chronic infection. This nutritionist uses fibrinolytics to help dissolve the fibrin in bacterial biofilms.

Turn to page 11 for more on Dissolve Biofilms with Fibrinolytic Enzymes.

Two Doctors Report on the use of Lumbrokinase in Lyme Disease: This Enzyme Complex Helps Potentiate Antibiotics and Antimicrobials

Lumbrokinase may help break up the biofilms in patients who don't seem to improve on antibiotics or herbal antimicrobials alone.

Turn to page 13 for more on Doctors Use Lumbrokinase to Help Conquer Lyme Disease.

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New Enzyme Complex Isolated From Earthworms Is Potent Fibrinolytic

Lumbrokinase Has Anti-Platelet, Anti-Thrombotic Activity

By Edwin Cooper, Ph.D., Sc.D., Distinguished Professor, Laboratory of Comparative Immunology at UCLA, Editor-in-Chief of eCAM, an Oxford University Press journal

When the rains surge through southern California, a confetti of earthworms is washed out of the soil. I lift the worms onto grass so they can find their way home—these creatures whose potent medicinal properties I have spent forty years studying.

The earthworm's antioxidant, immune-boosting, and clot-dissolving "medicine chest" is as powerful as that of any plant and even many pharmaceuticals. Earthworms have managed to survive for millions of years despite the constant threat of extinction by microbial pathogens. If we can begin to understand their remarkable capacities, we might design similar strategies to assist our own survival.

I have often wondered if earthworms are the creatures who first demonstrated a functional dichotomy in evolution: they evolved to be able to clean up the battlefield after having killed

In this update we report from leading researchers and doctors on the power of lumbrokinase to:

- dissolve clots and protect against ischemic heart disease and stroke
- lower fibrinogen levels in cancer patients, which is strongly associated in scientific studies with better outcomes, less metastasis, and slower growth of tumors
- dissolve bacterial biofilms present in chronic infections in conditions like autism and Lyme disease, allowing antimicrobials to work effectively
- offer antiplatelet, anti-thrombotic and anti-apoptotic activity, remarkably regulating hypercoagulation

foreign invaders. They have cells that, much to my wondering eyes, look very much like human natural killer cells and neutrophils when examined with cytofluorimetric analysis and microscopy. I may sound a little eccentric when I tell you that my excitement over my beloved creatures is immense—I believe they hold healing

treasures for us all.

In research I did in Modena in the late 1990's, I discovered that earthworm leukocytes can recognize human cancer cells as foreign and then kill them. Electron microscopy showed the astonishing "cinematography" of earthworm cells becoming incredibly active, throwing out "pseudopodia", and literally tearing apart cancer cell membranes from a human cell cancer line named K562. In fact, in all the time I've studied earthworms, I've never once been able to induce

cancer in them. I could irritate them only to the point that they formed inflammatory lesions.

As Charles Darwin once wrote, "It may be doubted whether there are many other animals which have played so important a part in the history of the world."

Note: Dr. Edwin Cooper, Ph.D., has been studying earthworm immunity since the 1960's. He is the author/editor of more than 25 books and several hundred publications on comparative immunology and invertebrate immune systems. He co-organized the International Symposium on Complementary and Alternative Medicine in Kanazawa, Japan, in 2002. He has been awarded *Docteur Honoris Causa* from five American and European universities and appointed Senior Visiting Scientist at the University of Bologna, Italy, in 2006.

Earthworms: Ancient Medicine, New Science

The last ten years have been a busy time for scientists exploring the medicinal treasures of earthworms. Laboratory, animal and clinical human studies have isolated enzymes and compounds that have proven to be potent fibrinolytics.

In healthy human volunteers, an enzyme complex isolated from earthworms increased levels of tissue plasminogen activator (t-PA) and consequently, fibrinolytic activity—without harmful side effects. In a study in 2000 the complex was found to be beneficial for ischemic stroke, without increasing the risk of excessive bleeding as other anticoagulants can. Using spectrofluorimeter and flow cytometry, a third study found that this complex has both anti-platelet activity (by reducing calcium release), anti-thrombotic activity (by reducing intercellular adhesion molecule-1) and anti-apoptotic activity (by inhibiting a specific pathway). All these activities, the researchers conclude, were “remarkably regulated.”

Earthworms have a long history in folk medicine—as far back as the 1300’s. In ancient Burma and Laos, smallpox victims bathed in water where earthworms had been soaked. Worms were boiled in water with salt and onions and the broth given to women with postpartum weakness or difficulty nursing. In Iran dried earthworms were prescribed to help treat jaundice, and American Cherokee Indians used earthworm poultices to draw out thorns. According to the most famous ancient Chinese materia medica, earthworms could treat hemiplegia (a condition where half of the body is paralysed), fever, and blood clots.

Worms produce unique and potent molecules. One of my first research papers proved that earthworms have an immune system powerful enough to destroy other earthworm allografts, xenografts, but never autografts (an autograft is your own body’s graft; allograft is a graft of foreign material from your own species; and a xenograft is a graft from another species, such as a pig heart valve into a human). Earthworms can kill bacteria and lyse foreign cells; their body fluid contains leukocytes that are as varied as those of many vertebrates. This is in spite of the fact that, unlike us, earthworms have no adaptive immune system, and do not form antibodies.

Lumbrokinase may be effective in the treatment and prevention of ischemic heart disease, myocardial infarction, thrombosis, and pulmonary embolisms.

Earthworms happily crawl and munch their way through garbage teeming with bacteria and fungi, and not only fight off infection but alter that garbage so that their nitrogen and mineral-rich castings transform it into fertile, oxygen-rich soil. And, as practically every curious child knows, you can slice some earthworms and they will regenerate.

In the last ten years a number of the earthworm’s clot-dissolving, lytic and immune-boosting compounds have been isolated and tested in laboratory and clinical studies. In particular, research has focused on clot-dissolving molecules. Fibrinolytic enzymes have been purified and studied from several species of earthworm, including *Lumbricus rubellus* and *Eisenia fetida*, and been found to be both potent and safe. This is very good news, since according to a 2008 conference report from the American Society of Hematol-

ogy, thromboembolism impacts over one million Americans a year and is responsible for more deaths annually than breast cancer, HIV and motor vehicle crashes combined!

The Key to Lumbrokinase: Active Only in the Presence of Fibrin

Lumbrokinase (LK) is a group of six, novel proteolytic enzymes derived from the earthworm *Lumbricus rubellus*. In a 1992 study, a crude extract of the worm was shown to have a potent thrombolytic effect. The heat-stable, purified enzymes were first isolated in 1992 by Japanese researchers. The enzymes have potent fibrin-dissolving properties (fibrin is a protein deposited to create a mesh around a wound), decrease fibrinogen (a protein produced by the liver that is involved in the clotting cascade), lower blood viscosity and markedly reduce platelet aggregation.

Recent research suggests that LK may be effective in the treatment and prevention of ischemic heart disease, as well as myocardial infarction, thrombosis of the central vein of the retina, embolism of peripheral veins, and pulmonary embolisms.

One key, remarkable property of lumbrokinase is that, unlike the medications streptokinase and urokinase, it is only active in the presence of fibrin. Though it dissolves fibrinogen and fibrin very specifically, it hardly hydrolyzes other important blood proteins such as plasminogen or albumin. It has the profound advantage of not causing hemorrhage due to excessive fibrinolysis. In fact, its plasminogen activator is remarkably similar to the plasminogen activator in the tissues of other species. Toxicological experiments have found

no negative effects of LK on nervous, cardiovascular, respiratory and blood systems of rats, rabbits and dogs. Long-term animal experiments show no damage to liver or kidney function, no negative influence on embryonic development, and no mutagenic effects in embryonic rats. LK has no negative effects on blood levels of glucose and lipids. And a 2001 study tested one of the six enzymes of LK to determine whether LK does indeed pass into the blood from the intestines while maintaining its biological activity. This research found that approximately 10% of the full-size enzyme could pass through the intestinal epithelium intact and into the blood. This is not surprising; research from The Hebrew University has shown that many peptides can pass intact and biologically active through the intestinal lumen into the blood.

In a laboratory experiment in 1994 from Seoul National University, lumbrokinase (the six enzymes) was extracted from the earthworm. LK was then immobilized onto a polyurethane surface to investigate its antithrombotic activity. Platelets adhered to the surface and then drastically decreased in number, suggesting that LK digested the fibrinogen and inhibited the ability of platelets to stick to the surface. Similar results were found with an experiment on a rabbit shunt in the laboratory; occlusion time was monitored and it was found that on shunts without LK, occlusion time was 32 and 42 minutes, respectively, but those with LK-immobilized polyurethane had an occlusion time of 140 minutes—as much as four times longer.

Such studies show the potential of immobilized-LK surfaces for eventual use in tissue transplantation. In one

remarkable 1999 study, Lumbrokinase was tested on LK-immobilized polyurethane valves which were then fitted to total artificial hearts in three healthy lambs. In the control lamb, the valves were untreated; in the second lamb, only valves on the right were treated, and in the third lamb, only valves on the left were treated. Implants were left in for up to three days. In the control lamb, thrombi were observed in the inlet parts of the valves. In the other two lambs, thrombi formed only on untreated control valves. Similarly, fibrinolytic activity was observed only in treated valves, and the proteolytic activity of the treated valves was three times higher than that of untreated valves.

Fifty-one stroke victims were treated with lumbrokinase; researchers concluded it is beneficial for ischemic stroke and does not increase the risk of excessive bleeding

A Potent Clot-Dissolver

Animal studies have demonstrated that LK is a potent clot-dissolver. A study in rabbits looked at LK's ability to dissolve an embolism in the pulmonary artery. The embolism was radioactively tagged, and blood radioactivity was tested 30 minutes, one hour, two hours, three hours, and five hours after LK had been administered. Radioactivity increased markedly at three and five hours, indicating that LK had begun to dissolve the embolism and disperse it into the bloodstream. In another study rectal administration of LK reduced the size of a thrombus in the inferior vena cava in rats. And in yet another 1998 study, freeze dried *Lumbricus rubellus* was given to rats orally, and then plasmin activity in the blood was measured. At half a gram of LK

per kilogram of weight a day, the activity doubled; at one gram, it quintupled. These results suggest that earthworm powder alone is valuable for thrombotic conditions. Finally, grafts treated with LK and inserted into the inferior vena cava of rabbits were compared to those not treated with LK, at five hours, 1, 2 and 4 weeks after implantation of the graft. Non-treated grafts were totally occluded with thrombus only five hours after implantation. LK treated graft were clear one week later, and those treated with a special covalent bonding method were clear four weeks later. Researchers concluded LK has potential antithrombotic effects in vascular prosthesis.

Lumbrokinase may help protect against myocardial ischemia and heart attack. A 2006 study in rats from Harbin Medical University in China induced heart attack in rats by permanently clamp-

ing shut the left anterior descending coronary artery. Lumbrokinase decreased the size of the infarct in a dose-dependent manner.

Human Studies Demonstrate Potency and Efficacy

Clinical trials in humans have been equally impressive. Research has found LK safe and effective as a thrombolytic in human volunteers. A hundred and twenty milligrams of freeze-dried earthworm powder was given orally to seven healthy volunteers aged 28-52 years old, three times a day for seventeen days. Blood was withdrawn before the trial to establish a baseline, and then at days 1, 2, 3, 8, 11 and 17. Fibrin degradation products, tissue plasminogen activator (t-PA) levels and activity were measured in the blood. The t-PA levels gradually increased through the

entire experiment. Fibrinolytic activity also increased.

In an even more significant study from Shanghai Medical University in 2000, LK was used in patients who had suffered a stroke. Fifty-one stroke victims were randomly divided into a treatment group (31) and a control group (20). The Chinese stroke score was used to evaluate the effect of LK. Several measures of blood viscosity were used—prothrombin time, fibrinogen content, tissue plasminogen activator (t-PA) activity, D-dimer level, and more. In the treatment group, t-PA activity and D-dimer level increased, while fibrinogen decreased significantly. Plasminogen activator inhibitor activity and prothrombin time were unchanged. Lumbrokinase inhibits the coagulation pathway and activates fibrinolysis by increasing t-PA activity. This suggests that LK is not only beneficial for ischemic stroke, but that it may not increase the risk of excessive bleeding as anticoagulants can.

This stroke study is backed up by a 2008 study from Harbin Medical University in China. Researchers wondered how LK might have an anti-ischemic action in the brain. Using spectrofluorimeter and flow cytometry, they found that LK has both anti-platelet activity (by reducing calcium release), anti-thrombotic activity (by reducing intercellular adhesion molecule-1) and anti-apoptotic activity (by inhibiting a specific pathway). All these activities, the researchers conclude, were “remarkably regulated by LK.”

Future Directions: A New Antimicrobial?

Do earthworms hold other treasures

for us? We know that plasmin has been implicated in wound healing, pathogen invasion, cancer invasion and metastasis. Might earthworms like *Lumbricus rubellus* also have antimicrobial and anti-cancer potential?

Preliminary research is intriguing. Lumbricin I is an antimicrobial peptide that has been isolated from *Lumbricus rubellus*. It exhibits antimicrobial activity against both Gram negative and Gram positive bacteria as well as fungi, yet without hemolytic activity against human blood cells. Lumbricin I is rich in proline and actually shares characteristics with peptides found in insects and fruit flies.

Using spectrofluorimeter and flow cytometry in humans, researchers found that lumbrokinase has anti-platelet, anti-thrombotic and anti-apoptotic activity

What about cancer? Earthworms are able to lyse and destroy foreign cells. As I mentioned at the beginning of this research review, I have been unable to provoke my earthworms into getting cancer. When earthworms are examined by electron microscopy their fabulous complexity is revealed. Researchers from Japan, Korea, China and Croatia have been studying how earthworm peptides may inhibit the growth of spontaneous tumors since the 1990's. One “killer” glycolipoprotein extract called G-90 retards tumor growth in mice. Lombricine, from *Lumbricus terrestris*, was purified by Japanese researchers in 1991, and was shown to inhibit mammary tumors in mice. Daily subcutaneous injections markedly slowed the growth of tu-

mors. Lombricine given orally as part of the diet also slowed the growth of tumors, though to a lesser degree than injection.

In addition, LK may help degrade and lyse fibrin clots from the venous blood of patients with malignant tumors. We know that cancer patients are at greater risk of clotting disorders, especially during treatment. According to research, malignant tumors secrete molecules that inhibit plasminogen activators and protect tumors. Might earthworm-derived enzymes like LK combat a tumor's protective mechanisms, and render it more vulnerable to treatment and to the innate immune system?

The Future of Earthworms as Medicine

We now know that earthworm enzymes and peptides may provide us with novel, potent and safe

approaches to the treatment of thrombosis. Since thrombosis remains the main cause of death in America despite available drugs, the potential of LK is enormous. I think back to my boyhood, when I refused to fish, so I would not have to inadvertently kill earthworms by using them as lure. But I never knew that my commitment to developmental biology and comparative immunology would lead me to study these simple, profound creatures.

References available at:

<http://www.nutricology.com/In-Focus-March-2009-Earthworm-References-sp-89.html>

Coming in the next issue of *In 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.

Cancer and Hypercoagulation: A Naturopathic Approach

How One Doctor Keeps Fibrinogen Levels Low in his Cancer Patients

Q&A With Naturopath Physician James Belanger, of Lexington Natural Health Center

In Focus: You are a naturopath focusing almost exclusively on cancer patients for the last eleven years. How did this come about?

Belanger: I had testicular cancer—which is supposedly a “good” cancer to have because it is often treatable. I had several surgeries and they said keep coming back to be monitored with catscans and checkups, but if the cancer recurred I’d have to undergo chemotherapy. I certainly didn’t want to do that and I knew that it can take a while before a recurrence actually shows up on tests. All kinds of bodily processes precede visible cancer growth—such as activation of the clotting cascade that allows angiogenesis and blood vessel growth. And so in working to keep myself healthy and free of any recurrences, I became more and more interested in helping others as well.

In Focus: Tell us about how you approach hypercoagulation and cancer.

Belanger: When I first see a cancer patient, I do a series of blood tests to look for growth factors in their blood that can influence the cancer. It is well documented in the scientific and clinical literature that cancer patients often have issues with hypercoagulation and even with excessive risk of blood clots.

(See sidebar Page 7: Hypercoagulation And Cancer). One important test measures fibrinogen levels in the blood.

In Focus: Why is fibrinogen so important?

Belanger: Fibrinogen is a protein made in the liver that plays a key role in blood clotting. Fibrinogen is a sticky,

A whole array of studies links excess fibrinogen and hypercoagulation with the spread of cancer. Excess fibrinogen can raise the risk of tumor recurrence.

fibrous coagulant in the blood, and there is a whole array of studies linking fibrinogen and hypercoagulation with the spread of cancer. Fibrinogen can raise the risk of tumor recurrence in several ways.

First, research shows that cancer cells can produce extra fibrinogen on their own. Second, when immune cells like macrophages infiltrate tumors to try and destroy them, the excess inflammation can cause the liver to make even more fibrinogen. So what does cancer do with all this extra fibrinogen? It uses it to grab hold of growth factors in the blood, like VEG-F and FGF, to help make blood vessels.

In addition, when there is excess fibrinogen in the bloodstream, red blood cells tend to aggregate in the tiny capillaries, creating areas of low oxygen tension (hypoxia). The hypoxia stimulates

the tumors to produce even more blood vessels, increasing the aggressiveness of the cancer.

So in general, fibrinogen helps enhance the metastasis of cancer. We know that fibrinogen is very useful in wound healing, and they say cancer is like a wound that doesn’t heal. Cancer and its surrounding tissues produce the same kind of inflammatory cytokines as a wound. These inflammatory cytokines attract macrophages, and stimulate the production and binding of fibrinogen. A wound uses the fibrinogen to bind VEGF and other angiogenic growth factors to help make blood vessels to heal the tissue. Cancer uses the angiogenic growth factors bound by the fibrinogen to grow and metastasize.

In Focus: So if you know that is cancer’s strategy, how do you thwart it?

Belanger: I measure fibrinogen levels and I put my patients who come back with high levels of fibrinogen on an enzyme complex called Lumbrokinase.

In Focus: What levels of fibrinogen do you consider too high?

Belanger: There was a really nice study in early stage stomach cancer that looked at the five-year survival rate and measured fibrinogen levels before surgery. The patients that had fibrinogen

levels between 180 and 310 had a longer five-year survival rate than those whose levels were over 310. And most labs say that 180 to 350 is normal and healthy. However, based on this study, if a cancer patient has fibrinogen levels over 310, I try to bring it down.

In Focus: What is the highest fibrinogen level you've seen in a patient?

Belanger: I actually have seen levels as high as 900 in some patients. There are certain cancers, such as pancreatic, colon and prostate cancer, where you can almost guarantee that fibrinogen levels will be high. I wish there were already a study that showed you can keep cancer patients in remission longer, or prolong life in and of itself, by lowering fibrinogen levels. I hope to publish my own data at some point, but all I can say right now is that I think it's a very important component to measure and address in every cancer patient.

In Focus: What amount of lumbrokinase do you prescribe to your patients?

Belanger: The dose depends on the level of fibrinogen they are starting out with. In a patient with a very high level of 900, I will start them on 80 milligrams of lumbrokinase three times a day. If that only brings down their levels by, say, a few hundred points I will add other supplements like resveratrol and indole-3-carbinol to bring it down more. I will also measure interleukin-6

in the serum and use supplements like Tauroximum if the patient's level is over 4 pg/ml. Interleukin-6 is a potent inducer of fibrinogen synthesis in the liver. I have been experimenting with layering different supplements. Once a patient is down to a safe level I keep them at that dose and keep rechecking their levels.

In Focus: Has anybody ever

I put my patients who come back with high levels of fibrinogen on an enzyme complex called Lumbrokinase. Lowering fibrinogen is very important in treating a cancer patient.

dropped too low?

Belanger: Occasionally I've seen someone drop to say, 150, when normal is 180 and then I decrease their supplements. Nobody has had any bleeding issues. I want to add something else about hypoxia that I didn't mention before. There are studies showing that tissue hypoxia decreases the effectiveness of radiation. Radiation needs oxygen molecules in order to work, it turns them into free radicals which destroy the cancer cells. So cancer cells in tumor areas that are hypoxic are going to be more resistant to radiation treatment. So that's another reason you want to lower fibrinogen levels. I look at lumbrokinase as a useful agent to help radiation work better. Even with chemotherapy, if the patient suffers from hypercoagulation that could impair effectiveness.

In Focus: Can you summarize your overall approach?

Belanger: Well, I've been at this for eleven years, and over that time I've become more successful. I've found out what works and what doesn't and I've found that each person is different. The same supplements don't have the same effect in each person. And I've discovered that certain supplements don't seem to mesh well. For instance, I don't know why but when I gave curcumin with R-lipoic acid, it didn't work anymore on inhibiting Interleukin 8 (another growth factor that I track).

In general, when I am able to improve various markers such as fibrinogen levels, my patients tend to report that their tumor has shrunk, or that—if they're in remission already—they have not had a recurrence. And conversely, when the markers are high, I do see more recurrences. I also look at levels of fibrin breakdown products, such as D-dimer. I add bromelain if a patient has a high level of fibrin breakdown products. When I use lumbrokinase and bromelain together, I will see D-dimer levels start to fall. I use resveratrol because I've seen that in menopause women's fibrinogen levels will go up, and so it seems that estrogen has an effect on fibrinogen. Resveratrol is a phytoestrogen. Basically, I'm trying to help my patients "beat" the catscan, trying to lower their risk level before something actually shows up.

Hypercoagulation and Cancer: A Look at the Latest Research

The body's coagulation mechanisms may play a part in the development and spread of some cancers, according to recent research. Fibrin, for instance, promotes the growth of tumors and usually surrounds malignant tumors, while fibrinogen allows tumors to acquire growth factors.

For years, medical researchers have noticed that the presence of blood clots may be a prelude to cancer, and in one Swedish study in 2000, men taking anticoagulants such as heparin seemed to be protected against developing prostate cancer. In fact, in an article from the Albany College

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of Pharmacy published in 2006, it was noted that “the coagulation system is activated in cancer and is further amplified by treatment with chemotherapy, radiation or surgery. Hypercoagulation is documented in virtually all cancer types...and is the second leading cause of death in cancer patients. The relationship between clotting activation and carcinogenesis supports the view of cancer as a hypercoagulable state.” And in a previous 2004 article from the same laboratory, published in *Cardiovascular Drug Review*, it was found that “Unfractionated heparin (UFH) or its low molecular weight fractions interfere with various processes involved in tumor growth and metastasis.”

Hypercoagulation contributes to a significant percentage of mortality and morbidity in cancer patients, according to an article in *Neoplasia* in 2002. “Prothrombotic factors in cancer include the ability of tumor cells to produce and secrete procoagulant/fibrinolytic substances and inflammatory cytokines...” the researchers report. “Other mechanisms of thrombus promotion in malignancy include nonspecific factors such as the generation of acute phase reactants and necrosis (i.e., inflammation), abnormal protein metabolism (i.e., paraproteinemia), and hemodynamic compromise (i.e., stasis). In addition, anticancer therapy (i.e., surgery/chemotherapy/hormone therapy) may significantly increase the risk of thromboembolic events by similar mechanisms, e.g., procoagulant release, endothelial damage, or stimulation of tissue factor production by host cells.”

A 2008 study by researchers in South Korea found that blood levels of coagulation markers such as prothrombin fragment F1+2 and D-dimer, and prothrombin time (PT), correlated with the clinical stage and lymph node metastasis of patients with operable gastric cancer. A total of 110 patients were studied. Plasma D-dimer and PT were highly correlated with the clinical stage of the cancer. Similarly, PT and F1+2 levels were significant in predicting the presence of lymph node involvement.

In a previous 2006 study at the University of Tokyo, excess levels of fibrinogen were associated with a worse clinical outcome in stomach cancer. A total of 405 patients with gastric cancer who underwent surgery were evaluated. There was a positive correlation between plasma fibrinogen levels and the depth of invasion of tumors. Lymph node and liver metastasis were also positively correlated with excess fibrinogen levels. The researchers concluded that “hyperfibrinogenemia is a useful biomarker to predict the possible metastasis and worse clinical outcome.” This research built on work from the University of Tokyo in 2005 that suggested that excess fibrinogen “may provide favorable circumstances for cancer cells to metastasize via the lymphatic system.”

A 2007 study of 105 patients with squamous cell cancer of the esophagus found that pretreatment levels of fibrinogen were correlated with prognosis. Researchers found that the plasma fibrinogen concentration (PFC) correlated significantly with the depth of invasion and with lymph node and distant organ metastasis. Patients with a higher fibrinogen level experienced a significantly worse overall survival.

Finally, a 2004 study from the National Cancer Center in Korea studied preoperative plasminogen levels in 354 stomach cancer patients undergoing surgery. “The plasma fibrinogen level was significantly lower in patients with early gastric cancer than in those with advanced gastric cancer...a significant relationship existed between the preoperative fibrinogen levels and the presence of metastatic lymph nodes and distant metastasis,” the researchers concluded. Once again, “these data suggest that the plasma fibrinogen level is a clinically important and useful marker of the extent of tumor progression in gastric cancer.”

What can we conclude? Fibrinogen levels are indeed an important marker in cancer and safely lowering fibrinogen may be useful.

— Abstracts —

J Gastroenterol Hepatol. 2007 Dec;22(12):2222-7. Pretreatment plasma fibrinogen level correlates with tumor progression and metastasis in patients with squamous cell carcinoma of the esophagus. Takeuchi H, Ikeuchi S, Kitagawa Y, Shimada A, Oishi T, Isobe Y, Kubochi K, Kitajima M, Matsumoto S.

BACKGROUND: Hypercoagulation has been reported to be associated with tumor progression and a poor prognosis in various carcinomas. In this study, we examined fibrinogen levels in pretreated patients with esophageal squamous

cell carcinoma (ESCC) and assessed its correlation with clinicopathological factors and prognosis in patients with ESCC. **METHODS:** Pretreatment fibrinogen levels were examined prior to surgery or other treatments (e.g. endoscopic mucosal resection and chemoradiotherapy [CRT]) in 105 patients with primary ESCC. We investigated the association of fibrinogen levels with clinicopathological background factors and the survival of ESCC patients. **RESULTS:** The plasma fibrinogen concentration (PFC) ranged from 209.4 to 781.6 mg/dL. Pretreatment PFC correlated significantly with the depth of invasion (T factor). There also existed a significant correlation between higher fibrinogen levels and lymph node metastasis (N factor) and distant organ metastasis. Patients with a higher fibrinogen level experienced a significantly worse overall survival ($P = 0.006$). Fibrinogen levels strongly correlated with platelet counts, white blood cell counts and tumor length. Pretreatment PFC were observed to have a significant correlation with CRT responsiveness in ESCC patients in stages II and III ($P = 0.005$). **CONCLUSION:** This study revealed that higher levels of fibrinogen correlated with tumor progression, metastasis and poor responsiveness to CRT in ESCC patients.

Jpn J Clin Oncol. 2008 Jan;38(1):2-7. Plasma levels of prothrombin fragment F1+2, D-dimer and prothrombin time correlate with clinical stage and lymph node metastasis in operable gastric cancer patients. Kwon HC, Oh SY, Lee S, Kim SH, Han JY, Koh RY, Kim MC, Kim HJ.

OBJECTIVE: The principal objective of this study was to determine the relationship between preoperative coagulation tests and the extent of tumor involvement in gastric cancer patients. **METHOD:** A total of 110 patients with adenocarcinoma of the stomach were studied in order to evaluate this relationship. Platelet count (P), prothrombin time (PT), activated partial thromboplastin time, D-dimer, fibrinogen degradation product, thrombin-antithrombin complex and prothrombin fragment F1+2 (F1+2) were evaluated. **RESULTS:** The D-dimer levels were positively correlated with the depth of invasion ($P = 0.007$). Plasma D-dimer and PT were highly correlated with degree of lymph node involvement ($P = 0.006, 0.004$, respectively). D-dimer level, PT and plasma F1+2 level were correlated with clinical stage ($P = 0.001, 0.017, 0.031$, respectively). PT and F1+2 levels were significant in the prediction of the presence of lymph node involvement on the multivariate logistic regression models (odds ratio 2502.081 (5.977-1047425.4); $P = 0.010$ and odds ratio 19.487 (1.495-253.936); $P = 0.023$, respectively). **CONCLUSION:** PT and plasma levels of F1+2 and D-dimer could be markers of degree or presence of lymph node involvement and clinical stage in patients with operable gastric cancer.

BMC Cancer. 2006 Jun 1;6:147. Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. Yamashita H, Kitayama J, Kanno N, Yatomi Y, Nagawa H..

BACKGROUND: Abnormal hemostasis in cancer patients has previously been described, however the correlation between the plasma fibrinogen level and cancer metastasis and prognosis has not been reported in a large-scale clinical study. **METHODS:** Preoperative plasma fibrinogen levels were retrospectively examined in 405 patients who underwent surgery for advanced gastric cancer. The association of fibrinogen levels with clinical/pathological findings and clinical outcome was evaluated. **RESULTS:** There was a positive correlation between plasma fibrinogen levels and the depth of invasion ($p < 0.05$). Hyperfibrinogenemia (>310 mg/dl) was independently associated with lymph node (Odds Ratio; 2.342, $P = 0.0032$) and liver (Odds Ratio; 2.933, $P = 0.0147$) metastasis, not with peritoneal metastasis in this series. Patients with hyperfibrinogenemia showed worse clinical outcome in T2 gastric cancer, however, there was no correlation of plasma fibrinogen level with prognosis in T3/T4 gastric cancer. **CONCLUSION:** Our results might support the idea that hyperfibrinogenemia can augment lymphatic and hematogeneous metastasis of advanced gastric cancer, which is major determinant of the prognosis in T2 gastric cancer. Therefore, in the situation without peritoneal involvement, hyperfibrinogenemia is a useful biomarker to predict the possible metastasis and worse clinical outcome in T2 gastric cancer.

Jpn J Clin Oncol. 2005 Oct;35(10):595-600. Hyperfibrinogenemia is a useful predictor for lymphatic metastasis in human gastric cancer. Yamashita H, Kitayama J, Nagawa H.

BACKGROUND: Although abnormal hemostasis has been described in cancer patients, the precise association between the plasma fibrinogen level and lymphatic metastasis has not been reported in a large-scale clinical study. **METHODS:** Preoperative plasma levels of fibrinogen as well as C-reactive protein (CRP) and carcinoembryonic antigen (CEA) were retrospectively examined in 649 patients who underwent surgery for gastric cancer, and the correlation between these

factors and nodal status was evaluated. RESULTS: Plasma fibrinogen level in patients with gastric cancer showed a positive association with nodal classification ($P < 0.0001$). Hyperfibrinogenemia (>310 mg/dl) as well as high CEA (>5 ng/ml) and CRP (>0.3 mg/dl) showed a significant association with nodal metastasis in univariate analysis. Multivariate analysis revealed that hyperfibrinogenemia had an independent association with nodal metastasis (odds ratio, 2.004 (1.140-3.521); $P = 0.0157$), whereas CEA and CRP were not independent factors. Hyperfibrinogenemia showed an independent association even in advanced cancer [odds ratio 2.611 (1.404-4.854), $P = 0.0024$, $n = 319$]. When the 649 gastric cancers were classified into intestinal-type and gastric-type adenocarcinomas, plasma fibrinogen level was correlated with nodal metastasis only in the intestinal-type. CONCLUSIONS: Our results suggest that hyperfibrinogenemia may provide favorable circumstances for cancer cells to metastasize via the lymphatic system. Preoperative plasma fibrinogen level is a useful predictor of lymphatic metastasis in intestinal-type gastric cancer.

Hepatogastroenterology. 2004 Nov-Dec;51(60):1860-3. Preoperative plasma fibrinogen levels in gastric cancer patients correlate with extent of tumor. Lee JH, Ryu KW, Kim S, Bae JM.

BACKGROUND/AIMS: The aim of the present study was to investigate the relationship between the preoperative plasma fibrinogen level and the extent of tumor involvement in gastric cancer patients. METHODOLOGY: Preoperative plasma fibrinogen levels of 354 patients who underwent gastric cancer surgery were quantified using an immunoassay. The relationships between the plasma fibrinogen level and other prognostic variables (tumor size, macroscopic and histological type, depth of tumor invasion, presence of lymph node involvement and distant metastasis) were then examined using univariate and multivariate linear regression analyses. RESULTS: The plasma fibrinogen level was significantly lower in patients with early gastric cancer than in those with advanced gastric cancer (312 ± 6.7 vs. 361.9 ± 97.0 mg/mL, $p < 0.001$). A significant relationship existed between the preoperative fibrinogen levels and the presence of metastatic lymph nodes (320 ± 78.6 vs. 352.6 ± 94.1 mg/mL, $p = 0.001$) and distant metastasis (338.2 ± 89.5 vs. 396.9 ± 128.3 mg/mL, $p = 0.013$). Size of the tumors and depth of tumor invasion could predict elevated fibrinogen levels positively in both the univariate regression and multivariate linear regression analyses. CONCLUSIONS: These data suggest that the plasma fibrinogen level is a clinically important and useful marker of the extent of tumor progression in gastric cancer.

A Special Note from Stephen Levine, Ph.D.

In November, 2002, we introduced remarkable new research on the fibrinolytic enzyme nattokinase. Our November, 2008 newsletter offered a detailed follow-up on the powerful properties of nattokinase, with field updates from expert physicians such as Martin Milner, N.D. and Jonathan Wright, M.D.

Nattokinase originated in Japan from the health food Natto, which is soy fermented by a special species of bacillus. Thousands of years of clinical use support the benefits of this health food and about a dozen published studies are available, largely from Japan.

This month, we offer you more detailed information on hypercoagulation and health, in relationship to the enzyme complex lumbrokinase, which is derived from the earthworm *Lumbricus rubellus*. Lumbrokinase is a complex of six enzymes, researched and widely used in China. The best studies on lumbrokinase originate in China where it

is an official medicinal used in many hospitals.

In this month's newsletter, distinguished professor of immunology Edwin Cooper, Ph.D., Sc.D., who has studied the medicinal properties of earthworms for 40 years, offers a detailed overview of research on lumbrokinase, and physicians report on their use of this potent enzyme complex in a wide range of clinical situations.

We believe that this information from your colleagues and from peer-review published literature is of critical importance to patient health.

We know of no solid, clinical, comparative data on lumbrokinase and nattokinase. When in doubt there is no reason that we know of (other than cost) not to try to use them together or to rely on patients' individual feedback to guide your choice between these two fibrinolytics.

Dissolve Biofilms With Fibrinolytic Enzymes: A Novel Approach to Chronic Infection in Autism Spectrum Disorders

In Focus: You have evolved a highly successful strategy to treating chronic bacterial infections and biofilms that involves some new insights and relies in part on fibrinolytic enzymes like nattokinase and lumbrokinase. I understand you are working with autism experts like Anjum Usman, M.D. and functional medicine pioneers to get the word out on your new insights.

Cohen: I do a tremendous amount of testing and assessing the children through urine and fecal analysis. What got me so interested in nattokinase and lumbrokinase was the concept of what a biofilm infection actually is. If you do a medline search on biofilms and platelet aggregation, fibrinogen, and fibrin, boom, it's there right in your face. Bacteria build biofilms by first aggregating together, and then rapidly weaving this protective web or matrix around them. They build a polymeric matrix. It's a sticky, gluey, mucus-y goop and it's got fibrin in it to give it an intact structure. The bacteria recruit fibrinogen to create fibrin as part of that matrix. At that point they can shed their outer membrane, which has the proteins that serve as antigens and as a target of the missile of the immune system. They're very protected. They're very crafty in creating a way to survive and procreate and hide from the immune system.

In Focus: Why are they protected, and how does that impact our health?

An Interview with Peta Cohen, M.S., R.D., founder of Total Life Center in Northern New Jersey. Cohen specializes in treating children with autism using a biomedical / nutritional model. Cohen received her Masters in Clinical Nutrition from New York University and has been a Defeat Autism Now! practitioner for the past ten years.

Cohen: They're protected because they've built this matrix but are still alive, still fermenting and metabolizing and leaching toxins into the bloodstream, although they may have a reduced metabolism compared to active, acute infection. Because of the biofilm they can no longer be reached by an anti-infectious agent or even the immune system. And because of the biofilm you may not find evidence of the infection in the fecal matter when you do stool cultures. For years, I knew from organic acid testing, from the short-chain fatty acids and metabolites the children were excreting, that they carried these infections. Yet when I did a stool culture I did not find the bugs.

In Focus: When you began to work at dissolving the biofilms, did you find the bugs?

Cohen: Oh yes! But I found something else that was just as fascinating, something nobody was thinking about. Think about what that biofilm might really be made of. The biofilm matrix has a horizontal and a vertical weave. It's

standard knowledge that biofilm bacteria sequester calcium, magnesium and iron to help build that matrix. Minerals give the biofilm integrity—as if you're building a wall. You don't only want bricks, you want cement. To address this, first you use fibrinolytics to help dissolve the fibrin, then you use EDTA to chelate out the minerals.

And guess what? We started getting huge dumps of toxic metal. Now why is that? I think the answer points to something so huge, whether we're dealing with autism or lyme disease or multiple sclerosis or lupus or even cancer.

In Focus: Why were the kids dumping toxic metals when you began to degrade the biofilms?

Cohen: Well, think about it. These are all positively charged cations, that's why EDTA is able to chelate them well. Mercury, and copper, and other heavy metals are also positively charged. Why would the bug preferentially insert calcium or magnesium? It could use any positively charged metal. This has been the most fascinating part of my year-long work on biofilms. As we degraded this biofilm matrix and liberated these bugs, not only did the organic acid levels get higher—one child bounced into the 400's—but the kids started to dump metals into the bowel. I felt like I'd exposed these little terrorists in a cell.

In Focus: So the metals and the

bugs are both in the gut?

Cohen: Right. At an Autism One Conference in Chicago last May, one researcher presented his proton analysis of brain tissue, attempting to verify the presence of mercury in the brains of autistic children, and he couldn't find it. Yet he still found evidence of activation of the microglia (a type of glial cell that acts as the first and main form of active immune defense in the central nervous system) as a consequence of toxic metals. So where are these metals? I'm suggesting they are in the biofilm, along with the bugs, in the gut. If the biofilm wasn't using toxic metals, along with common minerals, to build the biofilm, then why all of a sudden do I get these huge dumps of metals on stool tests?

In Focus: What exactly is your therapy and what sequence do you use?

Cohen: I start with enzymes like nattokinase and lumbrokinase, as well as other mucolytic enzymes, to get the best, broad fibrinolytic effect. Dr. Usman feels nattokinase is particularly good at degrading strep biofilms and I think that strep is a very big player in these children's health. I will run strep titers and they will be extraordinarily high. And these children—and certainly some adults as well—will manifest strep as a comorbid infection that has significant implications for neurological function. They will have very OCD type tendencies, and sometimes almost psychotic outbursts. There isn't a precise, sudden

onset with obvious symptoms.

In Focus: How much do you recommend?

Cohen: Remember, these patients are very young; some are just a few years old. So I will recommend half a capsule of each, two times a day. That would be a 50 milligram capsule of nattokinase, and a 20 milligram capsule of lumbrokinase. First do the enzymes along with EDTA,

"Because of the biofilm you may not find evidence of the infection in the fecal matter when you do stool cultures."

then thirty minutes later, add in an arsenal of antimicrobials. I use formulations containing berberine, artemisinin, citrus seed extract, black walnut hulls, artemisia herb, echinacea, goldenseal, gentian, tea tree oil, fumitory, gentian, galbanum oil, oregano oil, neem, and pharmaceuticals as well when necessary, such as Vancomycin, Diflucan, Gentamycin. I use a different one every day. Then an hour later you come in with the binders to help mop up the debris. I use chitosan, citrus pectin, a special bicarbonate formula, organic germanium, chlorella and others. I also use buffering agents, such as buffered vitamin C, since when the body is destroying bacteria it becomes acidic. Minerals must be assessed, and repleted when necessary. I test bloodwork and "pees and poos" (urine and stool) every two months to monitor the process.

In Focus: Enzymes, EDTA, antimicrobials, binders, and buffering agents. What are the clinical results?

Cohen: They're fantastic. It's like the missing piece. I had one little autistic boy who lives in the city who is loaded with viruses and infections and is now almost fully recovered. His mother used to complain about the terribly high levels of copper in his bloodstream and that his hair was like a copper mattress.

We measured the hair but there was a marginal amount of copper in it. He was not eliminating. As we got into the thick of the biofilms his copper blew out of his body

in his stool, for months and months. He'd been loaded with copper. I've had other children struggling for ages to get mercury out, and out it came.

In Focus: It sounds like this approach would work for any chronic illness in which chronic infection plays a role.

Cohen: Yes, I think biofilms are a huge missing piece in Lupus, Lyme Disease, Multiple Sclerosis and any autoimmune-type chronic infection. You have to ask, what compels the immune system to maintain this state of dysfunction? Ask yourself, how could an organism perceived by the immune system as foreign survive its presence? Either something has corrupted the immune system, or the organism has transformed itself in a way that the immune system can't find it. That's what the biofilm does. I believe it's one of the biggest medical issues we're dealing with today.

— Abstracts —

J Dermatol Sci. 1997 Nov;16(1):2-10 Biofilm formation of *Staphylococcus aureus* strains isolated from impetigo and furuncle: role of fibrinogen and fibrin. Akiyama H, Ueda M, Kanzaki H, Tada J, Arata J.

The formation of membranous structure (thickness from the plastic tissue-culture coverslip (hematoxylin-eosin) > 1 mm; periodic acid-Schiff-positive) was more prominent with *Staphylococcus aureus* (*S. aureus*) strains isolated from impetigo (coagulase types I.V origin) than with *S. aureus* strains isolated from furuncle (coagulase

type IV origin) ($P < 0.05$) in the plastic tissue-culture coverslip in human plasma after 72 h. Attachment of *S. aureus* cells to a plastic tissue-culture coverslip was more marked in 0-3% fibrinogen/tryptic soy broth (TSB) than in plasma ($P < 0.05$). The formation of the membranous structure was observed on the plastic tissue-culture coverslip with 0.3% fibrinogen/human serum but not with 0.3% fibrinogen + 5% glucose/TSB. Electron microscopy revealed abundant fibrin around *S. aureus* cells at 4 h and Ruthenium red-positive materials increased at 24 and 72 h in plasma. *Staphylococcus aureus* cell attachment to the plastic tissue-culture coverslip in plasma decreased by addition of levofloxacin (LVFX) at 1/2 minimum inhibitory concentration (MIC) and clarithromycin (CAM) at 1/4 MIC. Polysaccharide production of *S. aureus* cells on the plastic tissue-culture coverslip in plasma decreased with the addition of CAM at 1/4 MIC. Fibrinogen is closely related to initiation of infection but biofilm formation requires the conversion of fibrinogen to fibrin. Thus, attachment of *S. aureus* cells to the plastic tissue-culture coverslip, conversion of fibrinogen to fibrin by coagulase-prothrombin complex, and production of abundant glycocalyx by *S. aureus* cells are at least required for the production of biofilm in staphylococcal skin infection.

Appl Environ Microbiol. 2008 Aug;74 Fibrinogen induces biofilm formation by *Streptococcus suis* and enhances its antibiotic resistance. Grignon L, Grenier D.

In this study, we showed that supplementing the culture medium with fibrinogen induced biofilm formation by *Streptococcus suis* in a dose-dependent manner. Biofilm-grown *S. suis* cells were much more resistant to penicillin G than planktonic cells. *S. suis* bound fibrinogen to its surface, a property that likely contributes to biofilm formation.

Two Doctors Use Lumbrokinase to Help Conquer Lyme Disease This Enzyme Complex Busts Biofilms in Chronic Infection

— Marty Ross, M.D.: I Use It in My Toughest Cases —

I'm an integrative medicine doctor who set up and ran, as medical director, the nation's first publicly funded integrative medicine clinic in Kent, Washington. My practice partner is Tara Brooke-Nelson, a naturopath with a degree from Bastyr University. Both of us are very interested in the idea of bacterial biofilms as one phenomenon that blocks the ability of some of our patients to get well.

We are both using lumbrokinase to help break up the biofilms in patients who don't seem to improve on antibiotics or herbal antimicrobials alone. I lean more in the direction of antibiotics for Lyme disease

because they have more of a proven track record than herbs, but some of my patients prefer not to use conventional pharmaceuticals or just can't tolerate them. In that case I use one or more of four herbal antimicrobials: cumanda, andrographis, teasel, and cat's claw.

I prescribe one 20 milligram pill of lumbrokinase two times a day. I recommend this for patients who have been stalled for a while on more straightforward treatment and are not improving. I generally start to see improvement once I add in the lumbrokinase. I will even see herxheimer reactions when we finally add it in.

— Gary Sconyers, N.D.: It's Very Effective —

I'm a naturopathic doctor in Texas who uses lumbrokinase in all my lyme patients. I give patients up to 10 lumbrokinase capsules a day, in divided doses, three times a day. I also use nattokinase, in amounts ranging from 250 to 500 milligrams a day. In our most difficult lyme cases, lumbrokinase seems to work the best. I also use carinvora,

and herbal antimicrobials. I use herbs for liver detoxification. I recommend dietary changes. I had a lady in here who'd had lyme disease for twenty years. She had tried everything, and suffered from head to toe joint pain, brain fog and gut issues. She had gotten to the point where she'd given up. Now she is doing better than she has in decades.

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