



Focus

AllergyResearchGroup®

Allergy Research Group® Newsletter

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In This Issue

The NO/ONOO⁻ Oxidative-Inflammatory Disease Model . . .2

The NO/ONOO⁻ Cycle4

The Tenth Paradigm of Disease5

Ecklonia Cava: A Review . . . 6

Nano-Particle Chitosan: New Hope for Lyme-Related Herxheimer Symptoms by Steve Hines, N.D.9

The Power of Crab Shell: Chitin-Chitosan: Super Food / Super Tonic from Japan . . .10

Abstracts: Chitosan Oligosaccharides Demonstrate Clinical Effects In Animal Studies . .12

Martin Pall, Ph.D.: The NO/ONOO⁻ Oxidative-Inflammatory Disease Model (The 10th Paradigm Explaining Disease)

The NO/ONOO⁻ Oxidative-Inflammatory Disease Model (pronounced "No, oh no!") explains the initiation and chronic nature of fibromyalgia, chronic fatigue syndrome, multiple chemical hypersensitivity, post traumatic stress disorder, Gulf War syndrome and 14 other conditions.

There is a vicious cycle, involving elevated levels of primarily two reactive oxidant compounds in the body, nitric oxide (NO) and its oxidant product peroxynitrite (ONOO⁻). Once chronically elevated, these appear to act through known biochemical sequences to stay elevated. *For more on Dr. Pall's groundbreaking work, turn to page 2.*

"A brilliant treatise which brings us closer to a "unified field theory" explaining the underlying causes... and close to an effective treatment." - Jacob Teitelbaum, M.D., author and Medical Director of Fibromyalgia and Fatigue Centers

"A stunning expose, which is surely a central thesis of chronic, unexplained and fatiguing illnesses; namely that of oxidative stress mechanisms." - Paul Cheney, M.D., Ph.D., legendary CFS researcher

Ecklonia Cava Extract Found To Be Peroxynitrite Inhibitor, Super Antioxidant

The antioxidant capacity of *Ecklonia cava* extract (ECE) has been found to be many times stronger than green tea or other land-based polyphenols. Its peroxynitrite scavenging capacity, long half-life in the blood, and ability to pass through the blood brain barrier, explains much of its remarkable beneficial effects. (*see page 6*)

Detoxification With Nanomolecular Chitosan Found Helpful For Lyme Patients In Small Clinical Trial

Nanomolecular chitosan (NC) is known as a broad spectrum agent for detoxification. In contrast to its cousin, large polymer chitosan, NC is absorbed into the bloodstream and may be active in binding fat-soluble neurotoxins. A clinical report by Dr. Steve Hines, N.D. and background material is presented. (*see page 9*)

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The NO/ONOO⁻ Oxidative-Inflammatory Disease Model

Summarized from Dr. Pall's 2003 AAEM lecture & his new book *Explaining "Unexplained Illnesses"*

Many cases of the multisystem illnesses discussed in Dr. Pall's book *Explaining "Unexplained Illnesses"*, such as fibromyalgia (FM), multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), post traumatic stress disorder (PTSD), etc., are initiated by short-term stressors, such as viral or bacterial infection, physical or psychological trauma, or exposure to several classes of chemicals. Each of these stressors are known to stimulate responses that raise nitric oxide (NO) levels. They can all initiate the NO/ONOO⁻ cycle in a common way. The symptoms are generated by elevated levels of these oxidants and other consequences of the oxidant effects on inflammatory mediators. Therapy should focus on down regulating the NO/ONOO⁻ cycle biochemistry rather than on treating symptoms.

Multisystem Illnesses Share Common Etiology

Quite a number of researchers who work with this group of conditions have noted that they have multiple overlaps and have suggested that they might share a common etiology. Specifically, they have overlapping symptoms. Many people are diagnosed as having more than one. Cases of each of these are initiated by a short-term stressor, followed by the chronic condition, so there is a pattern of induction by a short-term stressor leading to a chronic condition in all of these diseases.

Gulf War syndrome (GWS) exhibits evidence of all four of the other syndromes, and Dr. Pall has proposed a common mechanism for all four. Donnay and Ziem stated that these conditions may reflect aspects of a common medical condition. Claudia Miller and others proposed that all four of these and some other diseases may share a common etiol-

ogy, which raises the question: Are we on the threshold of a new theory of disease (The Tenth Paradigm)?

The proposed etiology focuses on excessive levels of NO and its oxidant product peroxynitrite. NO does play important roles in the body, but excessive levels can lead to pathophysiology. NO can react with superoxide (both free radicals) to produce peroxynitrite, which is a potent oxidant.

The two tissues reported to be most active in producing NO are the brain and the immune system (radical production is part of the immune system's anti-microbial function). These are the tissues that are most often reported to be dysfunctional in these disorders. That is probably not a coincidence.

There are a number of short-term stressors that are presumably involved in inducing cases of these conditions. Commonly, CFS can be triggered by infection; FM is associated with a number of stressors, but commonly with physical trauma, such as an auto accident, a fall, etc.; MCS is triggered by chemical exposure; and PTSD is triggered by severe psychological stress.

So one must ask, how does a short-term stressor lead to a chronic medical condition? The proposal is that it initiates a vicious cycle mechanism involving excessive NO and peroxynitrite which perpetuates itself. For all of these conditions, one must distinguish between initial causes and ongoing causes. Ongoing causes involve the biochemistry and physiology that is being discussed. It is important to understand that there is a difference between the initial response



About Dr. Pall

Dr. Martin L. Pall, Ph.D., is Professor of Biochemistry and Basic Medical Sciences at Washington State University in Pullman, where he teaches medical biochemistry. His long term interests in biological regulatory mechanisms and in free radicals and reactive oxygen/nitrogen species have been key influences in leading him to this conceptual breakthrough in viewing multi-system illnesses. Dr. Pall is a member of the American Society for Biochemistry and Molecular Biology and is on the editorial board of the *Journal of Chronic Fatigue Syndrome* (Haworth). He is on the Scientific Advisory Board of Ariston Pharmaceuticals and the advisory board of the Environmental Law Centre in London, and has advised the South Australian government on multiple chemical sensitivity. Dr. Pall has published numerous papers on this topic over the past twelve years.

and the chronic condition: the initial changes from a short-term stressor can cause initial illness or disease. The chemistry associated with that is initiated after the stress is long gone, the symptoms can change in some manner and create long-term illness. The long-term effects are due to a vicious cycle of free radicals that has been initiated. The redox balance has been changed, the antioxidant reserves can become depleted, and excessive free radicals can lead to inflammation and further antioxidant depletion, and an ongoing cycle develops, and then you have a vicious cycle, and it is important to distinguish between the two.

For example, infection is associated with CFS and FM: infection induces elevated levels of inflammatory cytokines; those in turn induce the inducible nitric oxide synthesis iNOS; and that produces excessive levels of NO. We know that NO can react with superoxide, which is generated from the mitochondria and then by other mechanisms to peroxynitrite. Peroxynitrite is a very potent oxidant and produces a lot of oxidative damage. Potent oxidants can stimulate a transcription factor known as NF-kappaB, which can stimulate the synthesis of these inflammatory cytokines and the synthesis of iNOS itself.

So you can immediately see how the activity of peroxynitrite can lead to a

"Dr. Pall has integrated a massive amount of molecular biochemical data to present a well-crafted model which should CONVINCe SERIOUS MINDED SCIENTISTS AND DOCTORS that these conditions are strongly associated with reactive molecular fragments and oxidative free radical species, and that inflammation and immune abnormalities are the consequences."

Stephen Levine, Ph.D., CEO of Allergy Research Group
Author (with Dr. Parris Kidd) of the landmark textbook *Antioxidant Adaptation: Its Role in Free Radical Pathology*

potential vicious cycle, where levels of inflammatory compounds such as NF-kappaB are elevated, and in turn produce more NO.

We know that peroxynitrite can inactivate the manganese form of superoxide dismutase in mitochondria. With this enzyme damaged, superoxide will increase, which can lead to greater amounts of peroxynitrite.

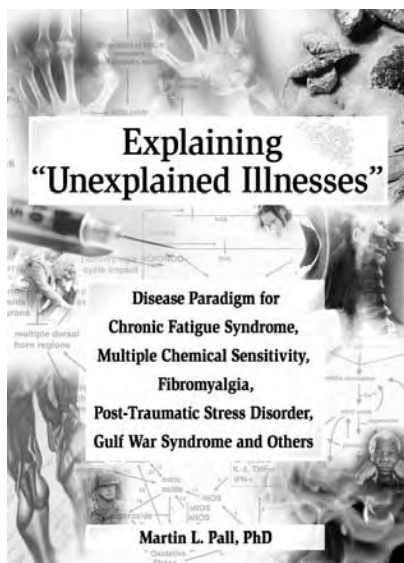
Peroxynitrite and NO itself can react with the mitochondrial electron transport chain and generate further superoxide generation. A number of additional biochemical mechanisms can be suggested which lead to a vicious cycle mechanism that chronically elevates these oxidants.

A number of studies show that drugs that increase NO, such as nitroglycerin and nitroprusside, increase NO synthesis in those tissues. You can test these tissues *in vitro*, and they produce

even more NO. In real live tissues, a vicious cycle can be generated. It is important to distinguish the difference between what the drug does directly (breaks down chemically to produce NO), and what the tissue response is (produces more NO enzymatically), and that distinction is what tells you there is a cycle present.

There are animal models for these conditions. For example, there is an animal model for MCS in which compelling evidence shows that NO has a role in producing the biological response. There is also an animal model for PTSD where NO plays a role.

Dr. Pall and colleagues have done studies on a drug called thiocetarsamide, which is reported to cure certain cases of chronic fatigue syndrome in animal models. These studies show that this drug is a scavenger for both NO and ONOO-, so this observation helps to support the model.



About The Book

Explaining "Unexplained Illnesses" provides long-sought explanations for the properties of chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia, post traumatic stress and Gulf War syndrome. This groundbreaking book examines common symptoms and signs; short-term stressors such as infection, chemical exposure, physical trauma, and severe psychological stress; why people are often diagnosed as having more than one of these illnesses, and approaches for treating the cause of each disease, rather than the symptoms. The book presents a detailed and well-supported mechanism [the NO/ONOO⁻ cycle ("No, oh no!")] that provides consistent explanations for many of the puzzling elements of these diseases. This unique book provides explanations for previously unexplained mechanisms with more than 1,500 references to scientific literature.

Dr. Pall's book is now available from ARG!

There is also data from animal models on MCS and PTSD, implicating excessive activity of the N-Methyl-D-Aspartate (NMDA) neurotransmitter receptor system. We know that when you have excessive stimulation of the NMDA receptors, that leads to increased synthesis of NO and ONOO⁻. So this is another mechanism in the model.

Dr. Pall has reviewed a substantial amount of evidence showing that in fibromyalgia patients, excessive NMDA activity is present.

The symptoms of these conditions can be very diverse. One major symptom is fatigue, which is characteristically found in illnesses associated with energy metabolism dysfunction. Hypoxia, ischemia, anemia, hypoglycemia, mutations that alter mitochondria function, etc., can predictably lead to fatigue. Fatigue is an inevitable consequence of energy metabolism malfunction. There is extensive evidence that peroxynitrite can lead to mitochondrial dysfunction and therefore energy metabolism dysfunction.

The immune system: is impacted by inflammatory cytokines and NO itself. The immune system cells are particularly sensitive to oxidative stress.

Learning and memory dysfunction: There are probably several mechanisms involved because NO has several functions related to learning and memory. If NO levels are elevated, then that would be expected to have an impact on learning and memory.

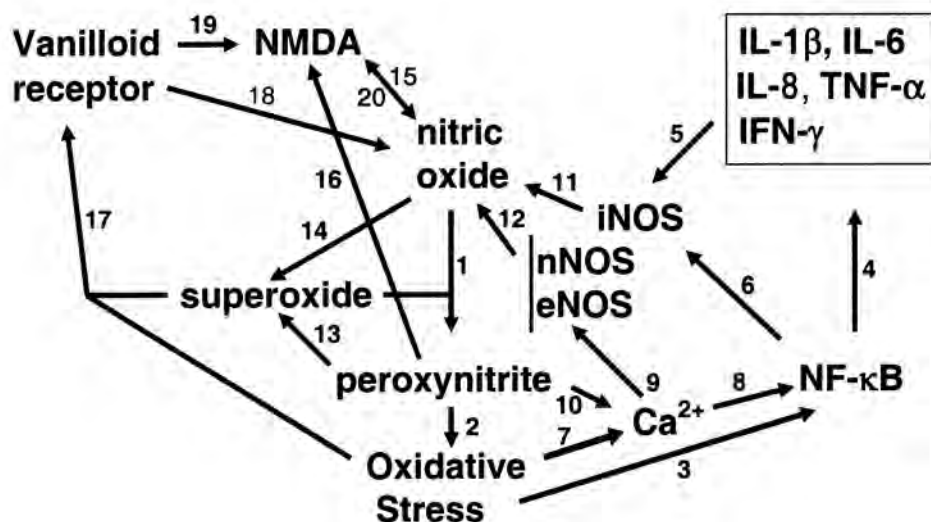
Orthostatic intolerance: NO can produce vasodilation both locally in the vasculature and through its effects on the sympathetic nervous system.

Pain: All the elements of the NO/ONOO⁻ cycle have a role in the excessive pain of hyperalgesia.

Depression: The NO/ONOO⁻ cycle produces inflammatory cytokines, and there is evidence that depression can be a consequence of that.

The NO/ONOO⁻ Cycle

The elevated nitric oxide/peroxynitrite vicious cycle (NO/ONOO⁻ cycle) predominantly involves those two compounds but involves many other elements. These include superoxide, intracellular calcium, the transcription factor NF-kappaB, inflammatory cytokines (upper right corner), oxidative stress, vanilloid receptor activity, and NMDA receptor activity. Mitochondrial (energy metabolism) dysfunction is also involved in certain pathways of the arrows. Each arrow represents the stimulation of one element by another, and the sequences of arrows constitute positive feedback loops that maintain the cycle.



The Tenth Paradigm of Disease

In the past 140 years, nine major paradigms of human disease have been postulated. These include:

1. Infectious Diseases
2. Genetic Diseases
3. Nutritional Deficiency Diseases
4. Hormone Dysfunction Diseases
5. Allergic Diseases
6. Autoimmune Diseases
7. Somatic Mutation/Selection Diseases
(Cancer results from a Darwinian evolution-like process of mutation and selection among cells of the body.)
8. Ischemic Cardiovascular Diseases
9. Amyloid (including Prion) Diseases
(such as Alzheimer's and Creutzfeldt-Jakob Disease)

Now, Martin Pall, Ph.D., has developed a TENTH PARADIGM of human disease to explain previously unexplained diseases. It also plays a role in many of the other nine paradigms:

10. The NO/ONOO⁻ Cycle Diseases

NO/ONOO⁻: Clinical Applications

The following is an excerpt from Dr. Pall's book Explaining "Unexplained Illnesses," from an extensive and valuable chapter on therapy for down-regulation of the NO/ONOO⁻ cycle:

At least 30 therapeutic agents or classes of agents are available today that are expected to down-regulate the NO/ONOO⁻ cycle biochemistry. Of these 30, clinical trial studies on chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and/or fibromyalgia (FM), have been performed on 12. All 12 of these showed evidence of efficacy in treatment of these multisystem diseases or closely related illnesses. Clinical observations and/or anecdotal reports suggest that 6 additional agents or classes of agents are also effective in treatment. None of these reach the effectiveness of a "magic bullet," providing, in most cases, only modest improvements. Given the complexity of the NO/ONOO⁻ cycle, this is not surprising. The question that must be raised is whether combinations of several types of these agents will be more effective than individual agents alone.

Five physicians have independently developed therapy protocols using from 14 to 18 agents or classes of agents

predicted to lower the cycle biochemistry. All five report substantial improvements in their patients. The patients involved in these therapies suffer from CFS, FM, chemical injury or unexplained chronic fatigue, and each of these types of patients show apparent substantial improvement. Two of these protocols have been tested and reported to be effective in clinical trials. It appears, therefore, that complex combinations of these agents are more effective than single agents in the treatment of these diseases.

Additionally, a number of prominent physicians have approached therapy for the multisystem diseases by treating with combinations of agents, many of which may be expected to down-regulate aspects of the NO/ONOO⁻ cycle. These include Drs. Paul Cheney (North Carolina), Grace Ziem (Maryland), Scott Rigden (Arizona), Jacob Teitelbaum (Maryland), Sarah Myhill (United Kingdom), Gordon Baker (Washington State), David Buscher (Washington State), and Nash Petrovic (South Africa). The clinical observations of each of them suggest that combinations of agents acting to down-regulate various aspects of the cycle may be more effective than are individual agents.

Ecklonia Cava: A Review

Highlights of the Many Benefits of *Ecklonia Cava* Extract, Super Polyphenol Antioxidant, Scavenger of Peroxynitrite, Inhibitor of NF-kappaB

Peroxynitrite scavenging and inhibition of NF-kappaB may account for much of the beneficial effects by ECE. This is consistent with the NO/ONOO⁻ theory.

SUPER ALGAE

- *Ecklonia cava* extract (ECE) is a standardized natural complex of unique marine molecules that originate from a specific species of brown algae (*Ecklonia cava*).
- ECE represents a unique category of polyphenols often called phlorotannins. Their unique polyphenolic structure endows them with biological activities that are not found in land-based plants.
- Dr. Haengwoo Lee and his team of M.D.'s and Ph.D.'s have spent over thirty million dollars on research.

SUPER ANTIOXIDANT

- ECE has up to eight interconnected rings, making its free-radical scavenging ability 10-100 times more powerful than other polyphenols.
- ECE is substantially more powerful than green tea catechins, which only have four rings.
- ECE is a marine-based polyphenol which is 40% fat-soluble, the half-life of ECE is up to 12 hours, compared to 30 minutes for water-soluble, land-based polyphenols.
- ECE has the ability to cross the blood-brain barrier.
- Peroxynitrite is the most notorious of the free radicals incriminated

by Martin Pall, Ph.D.'s groundbreaking research on multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome, post traumatic stress disorder, Gulf War syndrome, and fourteen other conditions. ECE has demonstrated potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite.

- NF-kappaB and other inflammatory mediators also play an important role in Dr. Pall's mechanism. ECE reduces tissue specific NF-kappaB.

FIBROMYALGIA

In an 8-week, double-blinded, placebo-controlled study of established fibromyalgia patients, ECE demonstrated beneficial results:

- **Reduced the time it took participants to fall asleep by 47 minutes**
- **Increased total nighttime sleep by 1.6 hours**
- **Improved soundness of sleep by 80%**
- **Boosted energy levels by 71%**
- **Participants reported 2 1/4 more good days per week**
- **Reduced pain by 31%**
- **General condition improved by 39%**

WEIGHT LOSS

- Dr. Lee found that ECE compounds inhibited DGAT more than 50%.

- In genetically caused obese laboratory rats, ECE reduced body fat and increased physical activity.
- In another study, ECE caused leanness and fat-resistance in animals given a high fat diet.
- 141 young adults were given a beverage containing ECE at 200 mg daily. In two weeks their average weight dropped nearly 2.5 pounds, muscle mass increased by nearly 2.5 pounds, and body fat dropped by 4 pounds, or 7.48%. ECE stimulates the body to burn fat by increasing muscle mass.

OBESITY

- ECE contains natural compounds capable of suppressing triglyceride synthesis, while promoting cholesterol removal and cardiovascular protection.
- ECE provides additional cardiovascular protection for obese patients prone to CVD and CHD through lowering LDL cholesterol and scavenging free radicals.

CARDIOVASCULAR BENEFITS

- ECE has been shown to improve coronary artery disease (CAD).
- Researchers found that ECE is even more potent at inhibiting the oxidation of LDL cholesterol than green tea catechins.
- ECE also reduces vascular inflammation by preventing oxidation, which also directly effects inflammatory mediators such as inflammatory prostaglandins, etc.

Cholesterol: 6-Week Clinical Trial

- Researchers gave 39 adults (average age 55.6) low dose (100 mg) ECE compounds for six weeks
- Their average cholesterol dropped from 228 to 224. LDL dropped from 141 to 135. HDL rose from 46.5 to 50.7 (highly significant).
- Triglycerides fell from 215 to 195, and the atherogenic index dropped 12.5%.

(Some of the parameters from the above study show very mild changes, which in themselves, may not be statistically significant. However, all parameters went in a health-positive direction.

Hypertension: 4-Week Animal Study

- Upon oral administration of phloretin (99.4%, 50 mg/kg) or enalapril (commercial hypotensive drug, 10 mg/kg) SBP dropped to as low as 160 and 140 mm Hg. Upon cessation of treatment, SBP increased again in both cases.
- Although ECE showed a similar pattern to the drugs, it also showed a slower rebounding of blood pressure during the no treatment period.

ACE Inhibition

- ECE tannins have been found to be potent natural ACE inhibitors, demonstrating more than 15 times the power to inhibit ACE as the most powerful land-based polyphenols.

Antiplasmin Inhibition

- ECE compounds are natural potent inhibitors of anti-plasmin, capable of efficient promotion of plasmin that performs fibrinolysis.
- ECE compounds have shown remarkable activity which is 40-

200 times greater than synthetic compounds Flufenamate and Chloramine T.

BRAIN FUNCTION: MEMORY, RELAXATION, ALERTNESS

- Dr. Lee's group found that ECE can increase the velocity of blood flow in the carotid artery from an average of 36.68 cm/sec to 40.09 cm/sec.
- An EEG study on brain waves of healthy middle age volunteers found that ECE compounds increase alpha-waves.
- ECE compounds were found to prevent sleepiness in bus drivers and in high school students during daytime activities.
- ECE has recently been found to protect neuronal cells from ischemia-induced inflammatory reactions which often occur in the aged and highly stressed brain.
- ECE compounds neutralize the neurotoxic free-radical peroxynitrite.
- ECE-treated mice showed substantial enhancement of acetylcholine in three brain regions related to memory formation, as compared with non-treated mice. Especially, 140% enhancement was observed in the frontal cortex that is crucial in long-term memory and associative thinking.
- In a mouse study, passive-avoidance memory testing was tested showing a 130-140% improvement.
- In rat study, ECE was found to inhibit beta-amyloid deposition in the brain. Beta-amyloid is the same substance that accumulates in Alzheimer's disease.
- The rats also learned maze challenges faster, which demonstrated

improvement in short-term memory.

ARTHRITIS, INFLAMMATION & NEURALGIA: ECE COMPARABLE TO CELEBREX®

- Dr. Lee and colleagues found ECE to naturally suppress inflammatory responses and neutralize inflammatory damage caused by reactive oxygen species.
- ECE's natural anti-inflammatory and tissue-protective properties appears to enable dramatic improvement in both arthritis and neuralgia.
- ECE's ability to treat arthritis was found to be comparable to Celebrex®, the prescription drug that reduces inflammatory cox enzymes.
- ECE compared almost identically to celecoxib (Celebrex) in the ability to reduce PGE2 by slowing down the lipoxygenase (LOX) system.
- Researchers recently studied ECE on 40 patients with neuropathy. ECE reduced nerve pain by 40% in four weeks. Overall, 80% of the patients responded favorably.

ALLERGIES / ASTHMA

- ECE appears to significantly relieve allergic reactions without drowsiness, dizziness and other side effects of anti-histamine drugs.
- Dr. Lee and his team found that ECE significantly reduced allergic inflammation in mice.
- ECE reduced the migration of eosinophils to the lungs by 75%. Inflammatory white blood cells (CD4+4 T Cells, resultant cytokines Il-4, 5, 13) were reduced by 50%. Mucus plugs in the airways were reduced by 75%. Airway epithelial hyperplasia reduced by

75%. Collagen-causing fibrosis in lung interstitium (fibrosis, airway remodeling) and smooth muscle cell thickness was reduced by 20% and 32%.

- These findings suggest that ECE compounds may prevent or reverse the progression of chronic lung disease such as asthma and Chronic Obstructive Pulmonary Disease (COPD).
- One of the ECE compounds (8,8-BE) significantly inhibits 5-LOX compared with other well-known natural medicinal compounds such as resveratrol and EGCG.
- The efficacy of ECE for asthma was demonstrated in an allergen-induced murine asthma mouse model by Dr. Emil Chi, Chairman, Department of Histopathology, University of Washington.
- The researchers tested an ECE product (KLS) in a mouse model of allergen-induced chronic lung inflammation and fibrosis. KLS was found to be effective in reducing allergic inflammation. KLS reduced the airway mucus plugging, and sub-epithelial fibrosis in the challenged mice.

ERECTILE FUNCTION ECE V. VIAGRA®

- Scientists studied 31 men with erectile dysfunction (ED) for over six months. They compared eight weeks of ECE use to Viagra®.
- The researchers looked at orgasmic function, intercourse satisfaction, overall satisfaction, and erectile function.
- ECE performed better than Viagra® in all parameters, except for erectile function, in which it

performed the same as Viagra®. No side effects were reported with ECE. See results below:

ECE Scores:

Orgasmic Function	87%
Intercourse Satisfaction	74%
Overall Satisfaction	62%
Erectile Function	66%

Viagra® Scores:

Orgasmic Function	27%
Intercourse Satisfaction	44%
Overall Satisfaction	39%
Erectile Function	66%

- The test population also had over 25% improvement in IIEF (International Index of Erectile Function) score, which was as high as 81%.
- Total IIEF score significantly increased from 29.1 ± 13.1 to 47.0 ± 14.5 with 62% of improvement.
- Scores on key questions regarding frequency of penetration and frequency of maintaining an erection after penetration were improved up to 74% and 77%.
- These results strongly indicate that the long-term administration of ECE significantly contributes to the neutralization of oxidative risk factors, thereby improving peripheral blood circulation around muscles and nerves involved in sexual function as well as the penile artery.

Nitric Oxide (NO)

- After a six-week study of ECE, flow mediated dilation and NO-mediated dilation increased by 60% and 50%.
- These results confirm that ECE can rejuvenate damaged endothelial cells to produce NO. (This effect was further confirmed in

the study on erectile dysfunction. Interestingly, Viagra® works by increasing NO in the penile artery.)

DIABETES

- ECE compounds have been found to be potent aldose reductase inhibitors, which may be of benefit for patients with metabolic syndrome, syndrome X, or diabetes.
- A mouse study showed that ECE reversed fat deposition in liver and pancreas cells.
- This same study showed that ECE served to markedly inhibit NF-kappaB inflammation in the pancreas.
- A recent Harvard (Joslin School of Diabetes) mouse study directly implicates excessive fat deposition in the mouse pancreas as turning on the NF-kappaB inflammation pathway, resulting in full-blown type II diabetes and insulin insensitivity in the mice.

SAFETY

- ECE is manufactured from edible algae through food-compatible processes.
- Tens of thousands of people throughout the world have experienced ECE in various forms of product without side effects.
- To date, Dr. Lee's team has not found any toxicity at any level.
- Several toxicity tests have been performed, and no adverse effects have been found at the effective human dose level of 1-10 mg/kg.

References available on request.

Nano-Particle* Chitosan

New Hope for Lyme-Related Herxheimer Symptoms

Steven Hines, N.D., N.E.
Hope Clinics International
San Angelo, Texas

Success rarely comes without a price, and treating Lyme disease and related complexes is no different. Often, the treatment may be worse than the disease. At our clinic in Mexico, we have been treating Lyme disease for many years. However, it seems the better we get at killing the spirochete borrelia, the more our patients hurt. I have read many books on Lyme disease, and most have a section regarding the dreaded Herxheimer reaction. One book goes so far as to say that the Herxheimer reaction is the symptom of a bad treatment protocol. I am not convinced, however, that those who claim to eradicate this miserable organism without pain are actually killing the organism. I believe they are only driving the organism into the cyst form.

I have my suspicions that homeopathic treatments for Lyme may do the same thing. We know that the organism quite readily reverts to the cyst form within two hours of being exposed to Doxycycline and many other antibiotics. I have seen many patients who have been "successfully treated" with antibiotics for their Lyme, but whose live blood showed massive amounts of cyst-form spirochetes even though their western blot Lyme test came back negative. Yes, their symptoms were indeed resolved, but possibly only because most of the spirochetes were driven into the cyst form. I can only speculate here, but spirochetes in cyst form may not produce toxins, replicate or invoke an immune response. All of this reinforces my belief in the adage, "No pain, no gain." We are not entirely without tools for the Herxheimer reaction. Among the useful tools are Vitamin C IVs, acetyl-L-carnitine, phosphocholine/serine/ethanolamine, lipoic acid, and all manner of TNF-alpha

inhibitors and zeolites. The zeolites have been the most beneficial until now, but we are still working handcuffed.

Nano-Particle Chitosan

We desperately need help in this area, which leads me to my enthusiasm about nano-particle chitosan. Earlier this year I was sharing some thoughts on the subject of neuroborreliosis with a colleague, specifically how some patients respond well and others not at all, even though they both have advanced Lyme disease. In recent years we have ordered some genomic tests on these patients, with some interesting findings. All but one of our neuroborreliosis cases have had a genetic defect in their ability to produce glutathione. Most notably, a Glutathione S-Transferase deficiency. Also, several have shown impaired ability to remove biotoxins. We believe deficiencies in detoxification may be the reason some Lyme cases have neurological symptoms more than others with seemingly comparable levels of infection. Either way, we have desperately needed something that could pass through the gastric mucosa and into the blood stream and the CNS to bind up the toxins. We've discovered something very powerful in this regard.

The compound is nano-particle chitosan (NPC). It differs from standard chitosan in that its particle size is small enough that it easily passes through the gut. We do not know if it passes the blood-brain barrier.

Small Clinical Trial

Following are the results of a small clinical trial of short duration. The product was in short supply at the time, so we used it sparingly. Each patient took one-fourth of a teaspoon three times a day for a week on an empty stomach. The product was encapsulated due to its

less-than-enjoyable flavor. One capsule contained one-fourth teaspoon powder. The patients ceased taking their zeolites during the trial.

Seventeen patients were chosen from our general population. All 17 were positive for *Borrelia burgdorferi*. Symptoms measured were: joint and muscle pain, sleep disturbance, headaches, depression, and fatigue. Three patients reacted immediately with allergy symptoms and ceased taking NPC immediately. All three patients said they had known shellfish allergies.

Number of patients with each symptom

Pain	8/17
Sleep disturbance	13/17
Headaches	2/17
Depression	3/17
Fatigue	10/17

Number of patients with improvement in each category:

Pain	8/8
Sleep Disturbance	10/13
Headaches	1/2
Depression	2/3
Fatigue	2/10

Pain

The most profound improvement was in the symptom of pain. All of the participants with pain reported improvement. Four of the eight said their pain was totally resolved. After cessation of the NPC, three of four said their pain returned. One patient reported no pain several weeks after cessation.

Sleep

The second most improved symptom was sleep. Most of the patients said they

*Also known as chitosan oligosaccharides.

slept deeply. Many woke in the same spot in which they fell asleep, indicating they didn't toss and turn. Some still woke in the night, but not as much as usual, and most reported waking much more rested.

Adverse reactions were few, withstanding the shellfish allergies. One patient said NPC "wired" her. Three patients said NPC had a Valium-like effect (the patients did not regard this as a negative reaction). Most patients reported feeling very relaxed. One patient said NPC provided a little too much relaxation.

Patient Report

One of the patients was a 32-year-old male with symptoms of multiple sclerosis with a positive Romberg test. His symptoms included disorientation and visual disturbance, primarily due to the neuroborreliosis, we believe. After three

months of treatment with cat's claw, IV ozone, high-dose vitamin C IV, two grams of Ceftriaxone twice daily, three milligrams of Neltrexone daily, a no-grain diet, and aggressive anti-fungal treatments (just a partial list), he was still walking into walls, stumbling, confusing his words, and experiencing extreme fatigue. We suspected that we were successful in killing the organisms but were still failing at removing the *borrelia* toxins from the brain. After administration of three capsules the first day, he reported sleeping like a baby and experienced major improvement in his pain. After four days he was able to walk a mile a day, and after 14 days he was walking three miles a day. We continued him on NPC because of his dramatic improvement. His cognition is much improved. He is now negative for Romberg, and his visual disturbance and disorientation have improved by 70 to 80 percent. This case is quite profound.

Patient Report

One of the patients was diagnosed with PTSD (Post Traumatic Stress Disorder). The patient reported an inability to sleep for six to seven days at a time, extreme anxiety, and outbursts of rage. After starting on NPC, he reported "feeling almost human." His sleep has improved as well as his anxiety and rage.

Standard Chitosan Not The Same

I have previously tested standard large-particle chitosan with lackluster results. The small-particle size seems to make a significant difference. Its sleep benefits alone are worth whatever it might cost. We have seen some very exciting results with NPC. We are looking forward to longer trials with a larger patient population. ■

Chitin-Chitosan: The Power of Crab Shell Super Food/Super Tonic from Japan

Akira Matsunaga, M.D., Ph.D.

Akira Matsunaga, M.D., Ph.D., is the first doctor in Japan to use chitin-chitosan in clinical practice. Here, we summarize some of the highlights of his in-depth book: *Chitosan, The Ultimate Health Builder*, copyright 1998, Vintage Press, New York, NY.

What is Chitin-Chitosan?

Chitin-chitosan (CC) is a mixture of chitin and chitosan. The chitin, the component of the crab shell, becomes chitosan upon enzymatic treatment.

Extraction Process

In order to extract only the chitin from crab shell, a chemical process is used consisting of 5% hydrochloric acid, which removes the calcium, and 5% sodium hydroxide, which dissolves the protein. If the chitin is deacetylated (by treating it with 45% sodium hydroxide (or caustic sodium) at a high temperature), chitosan is produced.

This treatment does not produce 100% chitosan, but in general, produces a mixture of 10-15% chitin and 85-90% pure chitosan, which is called "pure CC" (in the US, chitosan is a mixture of about 7% chitin and about 93% chitosan). Cost-effectiveness aside, the biological effects of chitin produced from all sources are the same.

Prehistoric Origins

As discussed in Dr. Matsunaga's book, chitin may be "the primordial form" of some of the first living things on earth, existing much earlier than dinosaurs.

Ancient Use

Chitin has been a part of Japanese folk medicine for thousands of years. Evidence that chitin has been used since ancient times can be found in *The Herb List*, the book of medicine from the Ming Dynasty, China: "Break a crab shell, grind it, make a ball out of it and eat it to treat anything that swells or grows."

Standard & Quality Control

Since chitosan became so popular so fast in Japan, the quantity and quality of chitosan can vary widely. For this reason, in 1995, the Japan Health Nutritious Foods Association announced "The Standard of Chitin-Chitosan Products".

What are Chitosan Oligosaccharides?

Chitosan oligosaccharides (CO) takes chitosan a big step further. When CC is ingested, a small amount of it is broken down into very small molecular particles by the enzymes of the body, thus producing CO. CO can also be manufactured by using an enzymatic process. CO is more easily absorbed by the body, but contains less fiber than regular CC, so the focus is more on its therapeutic actions.

Case Histories from Dr. Matsunaga

Akira Matsunaga, M.D., Ph.D., is the first doctor in Japan to use CC in clinical practice. Below are some of his case histories and observations.

Case History 1: Low Pulmonary (Lung) Function

The first patient Matsunaga tried CC on was his father, who suffered from diminished lung function as a result of lung surgery from tuberculosis thirty years previously. Matsunaga had already tried everything on his father, with no results, who was dependent on an oxygen tank and could only walk a few steps a day. After taking only two capsules twice per day (a total of 120 mg) for one week, Matsunaga's father was able to walk around the house without his oxygen tank. By the tenth day, he was able to leave the house and get off his meds, and enjoyed three years of improved health and quality of life before he died at age 81.

Case History 2: Skin Cancer

The next patient was a 75-year-old man with skin cancer on his ear. Again, Matsunaga had already tried everything, and the doctors were recommending that the ear lobe be removed. Matsunaga had the man take the same dosage he had given to his father (2 caps 2x per day). Within one week, the cancer began to shrink, and in four more days, it disappeared completely.

A Wide Variety of Health Conditions

Impressed beyond his expectations, Matsunaga soon implemented the use of chitosan on a much broader scale in his clinical practice with careful attention to detail. In general, he found that weak patients became stronger, and healthy patients became healthier; that often symptoms resistant to medications were alleviated; common daily complaints such as constipation, shoulder stiffness, low back pain, etc., disappeared; medication dosages were able to be reduced (by 30% on average), thus lessening their side effects; quality of life was improved in terminal patients.

Matsunaga found that chitosan did not target only one organ or disease, but that it was effective in a wide variety of health conditions including circulatory and heart diseases, dermatological diseases (atopic dermatitis, etc.), ophthalmological (eye) conditions, ENT (ear, nose & throat) conditions, hemorrhoids, and a multitude of problems affecting all organs of the body.

Government Funded Research

In 1982, the Japanese government, through the Ministry of Agriculture and Fishery, began a ten-year project to find ways to use "unused biomass" as large piles of unused crab shells were accumulating at the crab meat processing plants. A six billion dollar grant was funded by the Ministry of Education for "A New Extension of Basic and Clinical Researchers on Chitin-Chitosan and Their Enzymes", which prompted research at thirteen universities. The following are summaries of some this research:

Animal Studies: Cholesterol & Liver Health

Professor Shigeo Hirano, Tottori University, found that CC lowered cholesterol and neutral fats, and prevented liver dysfunction. In addition, the non-chitosan group showed inflamed and fatty livers, while the chitosan group's livers were completely normal.

Through various animal studies, Professor Michihiro Sugano, Kyushu University, found that CC absorbs LDL cholesterol and carries it out of the body through the intestines, as well as raising HDL cholesterol.

These findings have been clinically tested on many of Dr. Matsunaga's patients demonstrating cholesterol levels within normal range.

Cancer

Professor Shigeo Suzuki, Tohoku Medicinal College, found that "CC has anticancer action, preventing metastases of cancer cells." The study by Suzuki used the breakdown products of CC (chitin & CO), which were found

to strengthen macrophage and natural killer cells to kill cancer cells and increase immunity.

Professor Ichiro Azuma, Hokkaido University, reported that "chitosan is effective in inhibiting the metastasis of cancer cells." Azuma proposed that since cancer metastasis takes place by getting into the blood vessels, chitosan blocks pores on the blood vessel wall to prevent cancer cells from entering. He called it "The Theory of Cementing Molecules."

Professor Hiromichi Okuda, Ehime University, confirmed through animal studies that chitosan strengthens natural killer cells. In November 1993, he published his findings in the *Journal of Chitin-Chitosan Association*. In a rat study, Okuda found that the action of natural killer cells against cancer cells in the presence of chitosan was 4 to 5 times stronger than the controls.

Blood Pressure

Professor Hiromichi Okuda, Ehime University School of Medicine & Professor Hideo Kato, Hiroshima Women's University concluded "Chitosan lowers high blood pressure, and prevents it even with excess intake of table salt." But after this research was done, Professor Okuda and his group found that it was the chlorine in table salt, not the sodium, that causes hypertension. They gave alginic acid (a dietary fiber contained in Wakame seaweed) that binds to sodium, together with NaCl to rats. They found that even though the rats had excreted the sodium in their feces, they still had hypertension. The researchers then used chitosan to bind to only the chlorine and excrete it from the rats' bodies. Remarkably, the chitosan rats did not have hypertension. The researchers then confirmed their findings on themselves. They consumed a large amount of NaCl and ingested chitosan. They excreted only the chlorine in their feces and they did not get hypertension. They concluded that since chlorine is necessary to activate ACE (angiotensinogen-converting enzyme), which produces angiotensin that causes hypertension, the removal

Continued on page 14

Abstracts

Chitosan Oligosaccharides Demonstrate Clinical Effects In Animal Studies

The research on chitosan-oligosaccharide is extensive, and has shown numerous potential benefits for health. Here is a summary of the abstracts:

- Chitosan oligosaccharide can promote the growth of friendly bifidobacteria and lactobacillus. Unlike fructooligosaccharides (FOS), which promote the growth of only three probiotic strains, chitosan oligosaccharide supports almost all bifido- and lacto-bacillus species.¹
- Chitosan oligosaccharide has been shown to protect the liver from damage by carbon tetrachloride in mice.²
- Chitosan oligosaccharide has been shown to protect against mercury toxicity in mice.³
- In non-insulin-dependent diabetic rats, chitosan oligosaccharide had an anti-diabetic effect.⁴
- By preventing lipid peroxidation, and promoting activity of anti-oxidant enzymes, chitosan oligosaccharide maintained normal body and liver weight in mice poisoned with 2,3,7,8-tetrachlorodibenzo-p-dioxin.⁵
- Chitosan oligosaccharide has been shown to have antibacterial and immunostimulative effects against infection by *Staphylococcus aureus*.⁶
- Researchers could not find an acute or even subacute toxicity for chitosan oligosaccharide in rats. Any potential adverse effect, if it exists, is more than 2000 mg/kg in rats, which extrapolates to more than 135,000 mg per day for an average-weight adult human.⁷

#1 Chitosan oligosaccharides, dp 2-8, have prebiotic effect on the Bifidobacterium bifidum and Lactobacillus sp.

Lee HW, Park YS, Jung JS, Shin WS. Anaerobe. 2002 Dec;8(6):319-24

In order to investigate the prebiotic potential of chitosan oligosaccharide (COS), the effect of COS on bacterial growth was studied... The effects of COS on the growth of bifidobacteria and lactic acid bacteria were compared with those of fructooligosaccharide (FOS). FOS was found to have a growth stimulatory effect on only three strains: *Bifidobacterium bifidum*, *B. infantis* and *Lactobacillus casei*. However, COS stimulated the growth of most *Lactobacillus sp.* and *B. bifidum* KCTC 3440... These results demonstrate that COS has considerable bifidogenic potential... The present study shows that COS stimulates the growth of some enteric bacteria, and that COS has potential use as a prebiotic health-food.

#2 Protective effects of chitosan oligosaccharide and its derivatives against carbon tetrachloride-induced liver damage in mice.

Yan Y, Wanshun L, Baoqin H, Bing L, Chenwei F. Hepatol Res. 2006 Jul;35(3):178-84. Epub 2006 May 26.

The protective effects of chitosan oligosaccharide (COS), d-glucosamine (GlcNH(2)) and N-acetyl-d-glucosamine (GlcNAc)

on carbon tetrachloride (CCI(4))-induced hepatotoxicity and the possible mechanisms that involved were investigated in male ICR mice. CCI(4) (20mg/kg body weight, i.p.) administration induced marked increase in serum AST and ALT activities, primed liver lipid peroxidation, depleted sulfhydryl content, impaired total antioxidant capabilities and induced genotoxicity 24h after administration. Pretreatment with COS, GlcNH(2), and GlcNAc (1.5g/kg body weight, i.g.) for 12 consecutive days prior to CCI(4) challenge significantly induced metallothionein (MT) expression. Thus, the antioxidant defensive system in the body was strengthened to counteract the oxidative damage induced by the succedent CCI(4) administration. Serum AST and ALT activities were effectively decreased. Hepatic malondialdehyde formation was inhibited and sulfhydryl contents, total antioxidant capabilities were markedly restored. Genotoxicity as reflected by DNA fragmentation, however, was not mitigated by pretreatment with COS, GlcNH(2), and GlcNAc. Histopathologic results of liver also confirmed their hepato-protective effects. Pretreatment with COS, GlcNH(2), and GlcNAc also could significantly decrease serum creatinine and uric acid levels and inhibit lipid peroxidation in kidney homogenate.

#3 Chitosan oligosaccharide inhibits 203HgCl2-induced genotoxicity in mice: micronuclei occurrence and chromosomal aberration.

Yoon HJ, Park HS, Bom HS, Roh YB, Kim JS, Kim YH. Arch Pharm Res. 2005 Sep;28(9):1079-85. Erratum in: Arch Pharm Res. 2005 Oct;28(10):1203.

...To investigate the effect of chitosan oligosaccharide on mercury-induced chromosome aberration, mice in each condition were supplied with 203HgCl_2 and chitosan oligosaccharide ad libitum. Chitosan oligosaccharide significantly inhibited 203HgCl_2 -induced chromosome aberration in mice. Based on the results of this study, it may be concluded that the chitosan oligosaccharide is a nontoxic material that could be used as a suppressor of heavy metal-induced genotoxicity.

#4 Antidiabetic effects of chitosan oligosaccharides in neonatal streptozotocin-induced noninsulin-dependent diabetes mellitus in rats.

Lee HW, Park YS, Choi JW, Yi SY, Shin WS. Biol Pharm Bull. 2003 Aug;26(8):1100-3.

The antidiabetic effect of chitosan oligosaccharide (COS) was investigated in neonatal streptozotocin (STZ)-induced noninsulin-dependent diabetes mellitus rats. The fasting glucose level was reduced by about 19% in diabetic rats after treatment with 0.3% COS. Glucose tolerance was lower in the diabetic group compared with the normal group. After diabetic rats had been treated with 0.3% COS for 4 weeks, glucose tolerance increased significantly versus the diabetic control group, and glucose-inducible insulin expression increased significantly. In addition, fed-triglyceride (TG) levels in diabetic rats drinking 0.3% COS were reduced by 49% compared with those in diabetic control rats. The cholesterol levels of animals treated with COS were reduced by about 10% in fed or fasting conditions versus the corresponding controls, although the difference was not statistically significant. It was found that COS has a TG-lowering effect in diabetic rats, and that COS reduces signs of diabetic cardiomyopathy such as vacuolation of mitochondria and the separation and degeneration of myofibrils.

#5 Effect of chitosan oligosaccharide on 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced oxidative stress in mice.

Shon YH, Park IK, Moon IS, Chang HW, Park IK, Nam KS. Biol Pharm Bull. 2002 Sep;25(9):1161-4.

...Mice treated with chitosan oligosaccharide II were protected from TCDD-induced lipid peroxidation, inhibition of glutathione peroxidase and glutathione S-transferase activities, and losses in body and liver weights. These results suggest that chito-

san oligosaccharide might be a potential agent for combating TCDD-induced pathogenesis.

#6 The antibacterial and immunostimulative effect of chitosan-oligosaccharides against infection by Staphylococcus aureus isolated from bovine mastitis.

Moon JS, Kim HK, Koo HC, Joo YS, Nam HM, Park YH, Kang MI. Appl Microbiol Biotechnol. 2007 Mar 15; [Epub ahead of print]

Based on our previous study evaluating the *in vivo* cure efficacy of chitosan on bovine mastitis, a more water-soluble chitosan-oligosaccharide (OCHT) with a high degree of deacetylation and low molecular weight was prepared to obtain high antibiotic efficacy. The growth of *Staphylococcus aureus* isolated from bovine mastitis was inhibited within 10 min of treatment with OCHT in concentrations ranging from 0.0001 to 0.5%. Additionally, electron microscopic observation indicated that the surface of the OCHT-treated bacteria was expanded, distorted, and lysed compared to that of the control bacteria. In mice, the proportion of monocytes was elevated, and the levels of interleukin-6 and interferon-gamma sharply increased 1 h after the peritoneal inoculation of the OCHT (0.5 to 1 mg per mouse). Mice challenged intraperitoneally with *S. aureus* (2.5×10^8) colony forming units) after oral treatment with OCHT (0.5 to 2 mg per day) for 7 days showed a higher survival rate (70-100%) than that of the control (10%). We suggest that the OCHT prepared in this study is a potential agent for the prevention and treatment of bovine mastitis.

#7 Subacute toxicity of chitosan oligosaccharide in Sprague-Dawley rats.

Kim SK, Park PJ, Yang HP, Han SS. Arzneimittelforschung. 2001 Sep;51(9):769-74.

A subacute oral toxicity study of chitosan oligosaccharide was performed in Sprague-Dawley rats of both sexes. Each 36 male and female rats were administered by gavage with 500, 1,000 and 2,000 mg/kg/day for 4 weeks (7 days/week), respectively... In conclusion, it was suggested that subacute toxicity of chitosan oligosaccharide was low and the no-observed adverse effect level was considered to be over 2,000 mg/kg in rats.

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of chlorine by chitosan inhibits ACE activity, and therefore no hypertension results.

Infections & Inflammation

Kitazato University School of Medicine reported: "If chitosan derivative and collagen fiber are used to cover burn wounds, they prevent bacterial infection and inflammation."

Chitosan Binds to Heavy Metals

Chitosan binds very well to heavy metals and excretes them from the body. Chitosan's molecular weight is several hundred thousands to several millions. When chitosan binds to heavy metals, they cannot stay ionized, and become contained within the chitosan molecules. Pure chitosan is white or off-white, but when it is excreted bound to a heavy metal, it takes on the color of that metal. For example, copper comes out as dark blue, nickel comes out as light blue, cobalt – pink, iron – light yellowish brown, chrome – brown, etc. Dr. Matsunaga suggests

this could prove especially helpful for people who eat a high fish diet, such as the Japanese, who may be consuming higher amounts of mercury.

These heavy metal binding benefits extend beyond the human body. Since chitosan is a natural material with no toxicity, and large amounts of it do not have any negative effects on the environment, it can be used to treat heavy metals contained in the waste products produced by industry.

Safety

It is important to note that CC and/or CO may be contraindicated for those with shellfish allergies. Chitin is a safe, natural substance and is not manufactured with any synthetic chemicals.

Numerous experimental studies have been conducted by a number of Chinese institutions including The Department of Orthopedics of Changzheng Hospital under the Shanghai Second Military Medical University, the Department

of Health Toxicology of the Shanghai Second Military Medical University, the Shanghai Institute of Entomology's Chinese Academy of Sciences, the Department of Orthopedics at the Affiliated Hospital of Anhui Medical University, the University of Science & Technology of China, the Department of Orthopedics of Anhui Jiangong Hospital, and the Department of Health Toxicology of Anhui Medical University. Some of these studies include: heat source reflection, intracutaneous injection, skin sensitivity testing, systemic anaphylaxis test, eye conjunctiva and corneal test, hemolysis test, test of depressor substance, subcutaneous and endosteal implant test, mutagenic test, dominant lethal test, etc. Results have been consistent with reports from other international sources of no toxicity. In addition, the Japan Precision Chemical Corporation has conducted toxicity tests on CC, and has proven that it is safe. ■

Chitin-Chitosan Timeline

4000 years ago:	Crab shell was listed as a medicine in the legendary agricultural textbook of China.
14th–17th Century:	Crab shell was listed as a medicine in the Ming Dynasty herb list.
16th Century:	Crab & lobster shell tea was used as a folk remedy for maintaining or recovering health in various parts of the world.
1811:	French history professor Braconot isolated chitin from a mushroom and named it fungin.
1823:	French scientist Ogier discovered that chitin could be used to create external skin and named it chitin, which means envelope in Greek.
1859:	Rouge found chitosan.
1894:	Hoppe-Seyler named "chitosan."
1950:	USSR Medical Academy & Lichtenstein researched chitin-chitosan for military purposes.
1965:	Applications to agriculture and industry were made by the US & China to use chitin-chitosan.
1977:	The first International conference on chitin-chitosan was held in Boston, USA.
1982 (April):	Japanese Ministry of Agriculture and Fishery began a ten-year project of developing "Unused Biomass."
1982 (July):	The second International conference on chitin-chitosan was held in Sapporo, Japan.
1984:	Japan-American Seminar "The New Function of Chitin-Chitosan" was held at Delaware University, USA.
1985:	Japanese Ministry of Education gave scientific research grants to 13 universities for "New Developments of Basic and Applied Researchers on Chitin-Chitosan and Their Related Enzymes"
1985:	The third International conference on chitin-chitosan was held in Ancona, Italy.
1987:	The first popular chitin-chitosan book in Japanese Crab Revolution by Kesao Kaneko was published.
1991:	The fifth International conference on chitin-chitosan was held at Princeton University, USA.
1992:	Professor Okuda et al, Ehime University School of Medicine and Professor Kato, et al., Hiroshima Women's University reported chitin-chitosan's prevention of high blood pressure caused by NaCl (table salt).
1993 (March):	The National Institute of Health and Nutrition, Japan, confirmed chitosan's ability to lower cholesterol.
1993 (May):	Tottori Medical University and Unichika, Co. Ltd., Japan, started development of the anti-cancer agent Brachitin with the main ingredient being chitin.