

Cardiovascular Health

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# Townsend Letter

The Examiner of Alternative Medicine

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**Managing  
Cardiovascular Disease**  
A Guide to Nonsurgical Options



**What is 'Organic'?**  
Standards Losing Meaning

**Endurance Sports Risks**  
How Much Is Too Much?

**Chelation Therapy for Diabetes**  
An Important Complement

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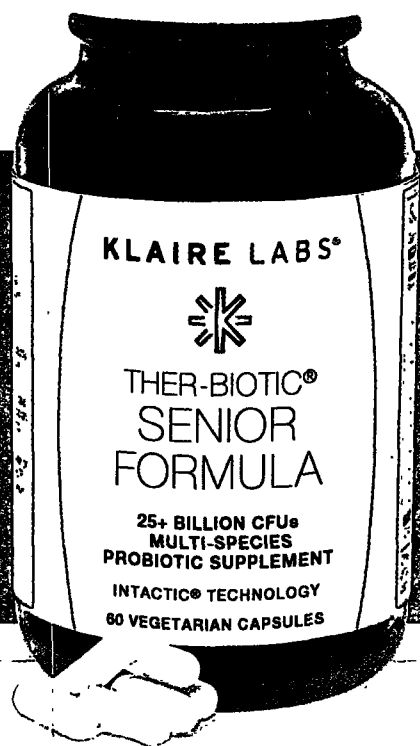
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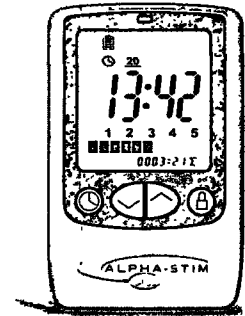


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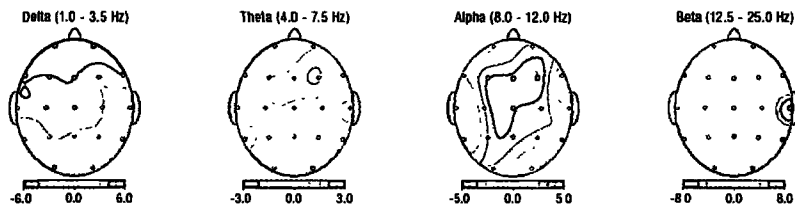
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\*Kennerly R. Changes in quantitative EEG and low resolution tomography following cranial electrotherapy stimulation. PhD Dissertation, the University of North Texas. 2006:529 pp., 81 tables, 233 figures, 171 references.





## From the Publisher

### Ebola and Measles

Two virus newsmakers, Ebola in 2014 and measles in 2015, both appear to be on the wane. Ebola is notably having a drop in its fatality rate, and there is no apparent explanation. Physicians who work for the international medical group Doctors Without Borders have observed that a higher percentage of treated patients are surviving Ebola – 50% instead of a 40% survival seen in 2014. Although there is greater organization administering hydration and other noncurative measures, workers do not believe that this explains the improved survival. Another

explanation is that Ebola has evolved or mutated, making it a less fatal infection, but genomic sequencing has not substantiated this theory. Nevertheless, the reduced fatality rate is welcome news for Ebola workers who have been struggling to contain the infection in Guinea, Sierra Leone, and Liberia.

On the home front, the incidence of measles appears not to be explosively increasing, a major worry of US authorities. The question of measles vaccination remains a chief concern both medically and politically. Public

*continued on page 6* ➤



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## Letter from the Publisher

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health strategy is heavily supporting new legislation mandating greater vaccination compliance and less opportunity for opting out. However, many libertarian-minded individuals as well as natural-health advocates object vehemently to mandatory vaccination programs. The social media are replete with reports testifying to the ineffectiveness of vaccination and concern about its medical risks and complications. Legislative efforts in California, Oregon, and Washington State all failed to increase mandatory vaccination rules.

Of particular concern to the readership of the *Townsend Letter* is the difficulty in being "open-minded" in this discussion; most parties are either all for or all against vaccination. Naturopathic physicians and integrative doctors should not be pigeonholed into making this an all-or-none position.

## National College of Naturopathic Medicine Visit

In February, after completing a continuing medical education course in Portland, Oregon, I visited with my wife, Deborah, the campus of the National College of Naturopathic Medicine. We were surprised to receive the red-carpet treatment by the school; we had thought we would enjoy a Friday afternoon having a short meeting with the president, David Schleich, PhD, followed by a tour. Dr. Schleich convened the academic deans for naturopathic education, Chinese medicine, and academic research. NCNM has had the longest-running four-year ND program of all naturopathic colleges. However, in the past decade NCNM has added certificate programs in homeopathic medicine, naturopathic obstetric-midwifery, integrative mental health, as well as advanced studies in classical Chinese medicine, qi gong, and

shiatsu. NCNM has opened a center for research that is actively pursuing grants for naturopathic research on and off campus. NCNM's medical clinic offers naturopathic treatment, Oriental medicine, and other clinical services while embracing insurance requirements with electronic medical records and coding. The campus has dramatically expanded in the past several years, occupying numerous buildings and grounds, including a convention center and alumni building in southwest Portland.

David Schleich has played a major role in the renaissance of NCNM during his past seven years as president. He was formerly president of the Canadian College of Naturopathic Medicine (CCNM) and before that executive of a health concern and an undergraduate college. Schleich is determined that a naturopathic college must be organic,

continued on page 8 ►

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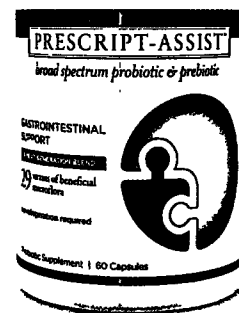
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<sup>1</sup>Pennisi, E. (2011) Body's Hardworking Microbes Get Some Overdue Respect. *Science*, 330 (December 2010), 1619



## Letter from the Publisher

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growing, and passionate in its pursuit of excellence. He is very strong in assessing financial matters and has actively brought in community leaders to help capitalize NCNM. Schleich has recruited new faculty, especially research members who are emphasizing the need for evidence-based study in naturopathic medicine. Still, Schleich's academic and business work are tempered by his earlier studies as a graduate student in English – he balances the academics with a need for play, especially music.

Deborah and I enjoyed our tour of the campus, particularly the library's collection of rare books curated by David's wife, Sussanna Czeranko, ND. Some of the readers may know of Sussanna and David by their writing in the *Naturopathic Doctor News & Review* (NDNR), wherein they have regular columns. Sussanna is a 1994 graduate of the CCNM and practiced naturopathic medicine in

Quebec and Toronto before coming to Portland in 2008. Sussanna's love of naturopathy's past has focused on preserving the writings of the old-time naturopaths from the late 19th and early 20th centuries. She particularly has enjoyed the writing of New York City naturopath Benedict Lust, who not only maintained long-standing naturopathic clinics and spas but also published his own journal of naturopathic treatment. Lust was a strong proponent of natural hygiene, especially hydrotherapy, applying hot and cold compresses alternatively. Authorities were not enthralled with Lust, and the medical establishment frequently reprimanded and jailed him. Czeranko is publishing the work of Lust and others in an 8-volume series on nature cure topics. The books are called the Hevert Collection and are the main publication of the NCNM Press. To order the first two books, *Origins of Naturopathic*

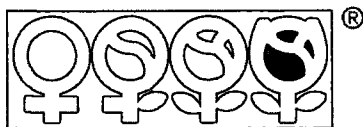


**President David Schleich, PhD, and  
Dr. Sussanna Czeranko**

*Medicine and Philosophy of Naturopathic Medicine*, see [www.ncnm.edu/origins](http://www.ncnm.edu/origins).

Deborah and I were also treated to dinner and hospitality at David and Sussanna's lovely home.

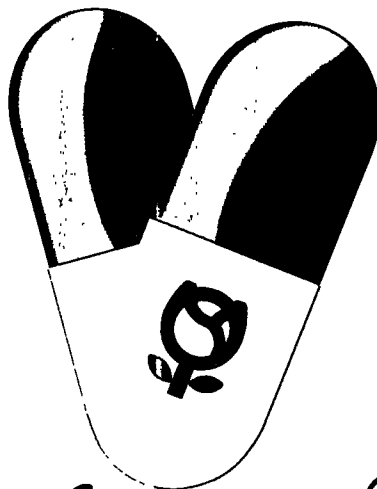
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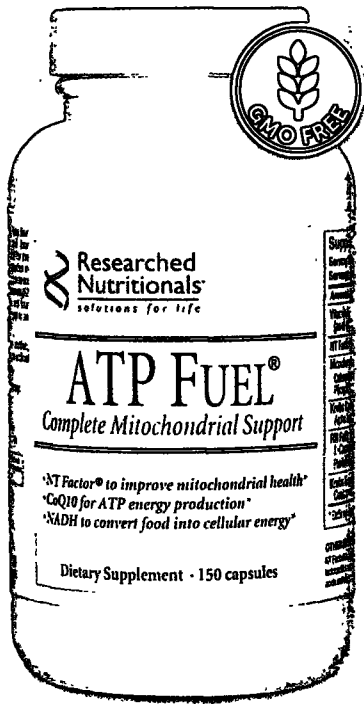
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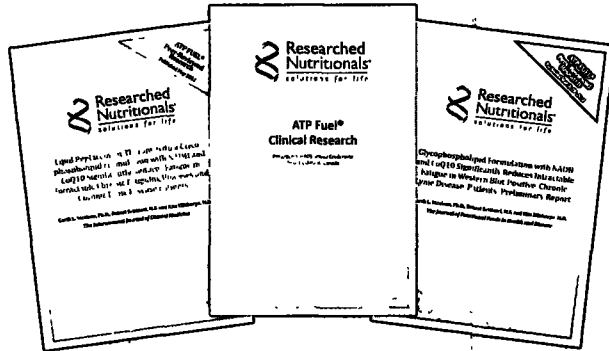


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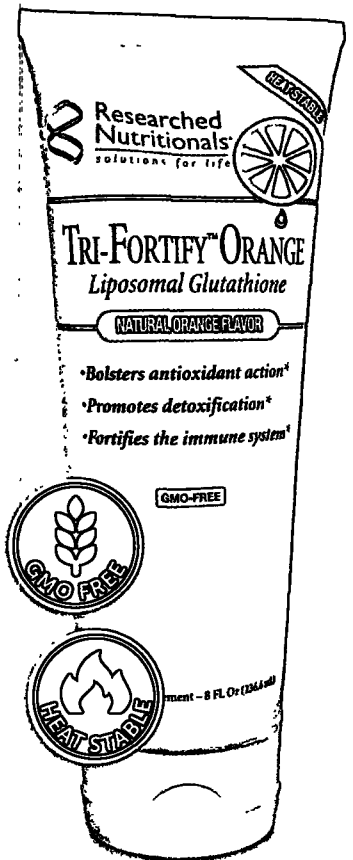
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**$\alpha$ -Cyclodextrin and Metabolic Disorders** | 34

by Stephen F. Olmstead, MD

Although the standard prescription of diet and exercise for managing these disorders sounds simple, it is easier said than done. Additional interventions are needed, such as increased intake of viscous soluble dietary fiber such as  $\alpha$ -cyclodextrin, now available as a supplement.

**Rauwolfia in the Treatment of Hypertension** | 37

by Douglas Lobay, Bsc, ND

This herb has been used in India for centuries to treat a variety of conditions. In this article, an experienced practitioner provides an outline for using it.

**Omega-3s' Therapeutic Impact on Eye Care** | 42

by John W. Lahr, OD, FAAO

Not only is the dietary ratio of omega-6 and omega-3 fatty acids important, so is the form and dosage. Read about how these and many other factors influence eye health and management of both anterior and posterior segment conditions.

**Complete Diabetes Care Now that We Have TACT** | 46

by L. Terry Chappell, MD; T. Rae Neal, MSN, CNP; and Natallie Paphanchith, MSN, ACNP-BC

For decades, chelation therapy has been ridiculed by "quack busters." New evidence from a major study helps legitimize this helpful treatment as part of a comprehensive integrative approach to diabetes.

**Managing Cardiovascular Diseases: Ramblings of a Maniacal Frenetic: Pragmatic Reflections on Helping Patients Understand Their Illnesses and Treatments** | 54

by John Parks Trowbridge, MD, FACAM

This thorough article provides an overview of the types of CVD and effective ways to treat it, starting with going back to the basic, but often overlooked, questions.

**Can Endurance Sports Really Cause Harm?**

**The Lipopolysaccharides of Endotoxemia and Their Effect on the Heart** | by Gary Huber, DO, AOBEM | 64

While there are many benefits to aerobic exercise, intense levels of activity have their risks as well. If you or your patients participate in marathons or triathlons, here are some suggestions to minimize those risks.

**Comprehensive Cardio Lab Work: An Interview with Decker Weiss, NMD, FASA, and Christina Cowger** | 70

by Nancy Faass

For decades, lab work in the case of heart conditions was difficult to access. Now these tests are more accessible than ever and can show results fast – helping motivate patients to stay on track.

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by John D. MacArthur

Preeclampsia is a pregnancy complication with no known cause. Is there an important connection to the prenatal ingestion of fluoride?

**Neural Prolotherapy: An Effective Pain Therapy** | 80

by Jeff Harris, ND

This therapy, simple and beautiful, is easily the most important advance in pain treatment and diagnosis in a long time. With training, the practitioner quickly learns the most effective ways to treat any pain condition.

**FCT Documented Case of an Apparently Reversed Heart Disease in a Junk-Food Addict with Obesity Diabetes, Thanks to Cause-Based Approach to Chronic Diseases** | 84

by Savely Yurkovsky, MD

In this impressive case study, a patient fends off illness for years, even decades, through bioresonance testing and treatment, even while maintaining an unhealthy diet.

**Roman Horror-Day: Organic Standards Take a Beating at Codex**

by Scott C. Tips, JD | 88

Sadly, consumers of "organic"-labeled produce will need to be ever more vigilant, as the definition of this term continues to be eroded by governments and other institutions.

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# Townsend Letter

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## Letter from the Publisher

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### Psilocybin with your Hospice Care?

Ever since the Nixon's administration's ban on psychedelics in the early 1970s, research in the use of LSD and psilocybin has been prohibited due to their Schedule I classification by the DEA. In the 1950s and later in the 1960s, when recreational use was ubiquitous, researchers found that psychedelic agents were beneficial in treating addiction, depression, anxiety, and existential difficulties. For more than three decades, the early experiments, not hippie trips, by scientists lay buried in abandoned journal archives. However, in July 2006, Roland Griffiths, PhD, a highly regarded neuroscientist at Johns Hopkins, published a paper with his colleagues in *Psychopharmacology* titled "Psilocybin Can Occasion Mystical-Type Experiences Having Substantial and Sustained Personal Meaning and Spiritual Significance." Unlike the work done in the 1960s, Griffiths's double-blind study used 36 volunteers who had never experienced a psychedelic drug and "treated" them with either psilocybin or Ritalin as a control, then repeated the study reversing the drugs used in each group. The individuals receiving psilocybin, but not the Ritalin group, experienced as a whole a significant mystical experience. Further, most of the individuals felt that the experience was among the most meaningful experiences of their lives, comparable to experiencing the birth or death of a loved one. When these individuals were asked to comment about how the psilocybin experience affected them a year later, most felt that it remained among their most meaningful experiences and continued to affect their lives. It should be noted that Griffiths's group needed to convince skeptical physicians and researchers at the DEA, FDA, and numerous research review boards at Hopkins. They had no journal articles to support their research hypotheses except what had been "unearthed" 30 years earlier.

Armed with this respected study, researchers at New York University School of Medicine, Tony Bossis, PhD; Stephen Ross, MD; and Jeffrey Guss, MD, who had organized a "reading" group on psychedelic research, decided that they would design a study to determine if psilocybin would affect anxiety and "existential distress" in cancer care. While Griffiths's work did pave the way for the NYU workers, convincing the IRB groups and the DEA and FDA was no cakewalk. However, in 2010, they had successfully organized a clinical study at NYU. A journalist, Patrick Mettes, entered the study after reading a newspaper ad for volunteers; he had advanced liver cancer and was faring poorly on chemotherapy. Mettes documented his experience receiving psilocybin and the 17 months that followed until his death. Mettes experienced a profound change in his overall mental well-being, despite the fact that the cancer continued to advance. He spent nearly every day "living" to enjoy what people and life offered him rather than just "dying" from the cancer. A week before he died, he gathered friends and family and staff at the hospital and shared with everyone his "joy" and "happiness" – it was a remarkable event.

Psilocybin is not a self-help treatment, at least not at this time. In the NYU study, the patient is brought into a clinical setting, and after the psilocybin is given in the morning the patient is observed by "guides" who assist with whatever problems arise. There are individuals who become agitated after using psilocybin, what may have been termed in the 1960s a "bad trip," but despite experiencing shocking imagery, hallucinations, or dying, the individual is helped by the guides to get through it. Usually after 6 hours, the psychedelic unreality ends, and returning to reality might be accompanied by a headache. However, the overall experience, a mystical state persists, and the patient now confronts his/her cancer transformed.

An editorial in the January 2015 *Lancet* supports further psilocybin and LSD research. The possibility that these agents may dramatically counter cigarette, alcohol, and drug addiction looms as breakthrough medicine. Even more significant is the possibility that these agents may counter depression far more dramatically than antidepressants.

Please read Michael Pollan's article, "The Trip Treatment," in the Feb. 9, 2015, *New Yorker* for a compelling read about psychedelic research.

### Chelation Revisited

Two of the articles in this issue are from colleagues who have shared my interest in chelation therapy since the 1980s. John Trowbridge, MD, and Terry Chappell, MD, have endured the longstanding derision of skeptical cardiologists and self-serving "quack busters" who have dismissed chelation as ineffective and dangerous. Too bad for the critics (including Wikipedia); the NIH-sponsored TACT published in 2013–2014 demonstrated no major adverse events. Additionally, the multicenter study revealed substantial cardiovascular benefits, including a reduction in myocardial infarcts, cerebrovascular events, and cardiovascular-related deaths. The TACT report revealed that chelation offered even greater benefit to patients suffering from diabetes. Chappell et al.'s report on "Complete Diabetes Care Now that We Have TACT" provides a rationale for making chelation therapy an important part of the overall treatment program in diabetic patients.

Trowbridge, author of *The Yeast Syndrome* and *Chelation and Other Detox Methods to Save Your Life*, titles his article "Ramblings of a Maniacal Frenetic – Pragmatic Reflections on Helping Patients Understand Their Illnesses and Treatments." This article has been on the "drawing board" for quite a period of time, and when he submitted it a year earlier, we deferred its publication. Trowbridge attempts in this lengthy report to put together a no-holds-barred guide to managing cardiovascular disease and other chronic illnesses. He makes the case that while medicine emphasizes diet and exercise, there are important nonsurgical and nonmedical interventions that must be made to rescue the patient from impending medical emergency. Chelation, treating chronic infection, removing toxic burden, improving oxygenation, and restoring mitochondrial functioning are critical early interventions.

Jonathan Collin, MD

# 'Annual Updates in Environmental Medicine' 2015: Poor Choice in Names but One Useful Conference!

by Jacob Schor, ND, FABNO

The naturopathic profession has a fundamental problem when it comes to naming things. Start with the very name of the thing that we practice, *naturopathy*. If the name's root words, *nature* plus *pathology* held true, we should specialize only in diseases that result from nature, ailments such as sunburn, heat stroke, or frostbite. A similar naming problem exists for the naturopathic specialty "environmental medicine." That name suggests to me that this specialty is about prescribing specific environments to serve as medicine. For example, an environmental medicine specialist might tell her patient, "Your vitamin D levels are low, causing osteoporosis; I am prescribing a month on a beach in Hawaii to soak up sun."

The reality is that environmental medicine is really about environmental toxicology, the study of toxins in the environment and the diseases that they cause. The original poster issue of environmental toxicology (or environmental medicine, if you prefer) is the past practice of adding lead to gasoline to improve automotive performance, a practice that unwittingly dispersed toxic amounts of lead into the environment, resulting in widespread health damage.

I suspect that naturopathic doctors have a special affinity for environmental medicine because many of us are ardent practitioners of homeopathy. *Homeopathy* is another name that isn't perfect. Sure, the root word *homeo* refers to that simillimum thing of Hahnemann's, the "like cures like" part of homeopathy, but there's no mention of an important detail: the hyperdilution of homeopathic remedies. Surely any name that describes what we call homeopathy

should include a Latin term like *minisculis* or *invisibilis* as part of its name. But enough sidetracks; let's go back to environmental medicine.

It is our familiarity with the action of hyperdilute homeopathic medicines that makes environmental medicine seem so very plausible to us naturopaths. In comparison with 30c, 200c, or 1 M dilution, the parts per million or even parts per billion of toxic substances that we are worried about in environmental medicine seem like massive amounts of material.

These thoughts came to mind while I was walking on a Florida beach last January. I was attending the annual conference on environmental medicine organized by naturopathic physicians Walter Crinnion and Lyn Patrick though their organization SpiritMed. This organization is a manifestation of Crinnion's desire to educate health-care providers on environmental medicine. He started the group back in 1999 and a year later began offering a 6-month training program. Enough people have completed this basic training program that there was a need, or shall we say an audience, for some form of regular update and more advanced training.

The first of these, "Annual Updates in Environmental Medicine," was held in January 2012 and then yearly ever since. The 2015 conference that I attended was in St. Petersburg, Florida, at a beachfront location where the offshore breeze kept the air feeling fresh; I came home with a lovely collection of seashells and a bit of a tan. This conference was both my first environmental medicine course and also my first time in Florida. Both were interesting experiences.

The conference was long, starting on Thursday morning and running

through lunch Sunday. Environmental-medicine conferencegoers are a bit geeky, quite comfortable juggling statistics, percentiles, p-values, quintiles, and associations. You need to remember your college statistics to follow some of the discussion. This wasn't the touchy, feely, mind-body exploration conference. The practice of environmental medicine relies on the hard sciences, even if the amounts of material are small.

Dr. Crinnion wrote me his reason for promoting this field of specialty: "Since Naturopathy holds dear to the principle of 'tolle causam,' it is critical to provide to our colleagues the symptomatic picture of toxicant-induced illness so that we may all properly address the main underlying cause (or causes) of disease."

For a good part of the four-day conference Drs. Crinnion and Patrick took turns at the podium. The exception was Friday, day two, when there were five guest speakers.

In regard to the topics and also these guest speakers, Dr. Crinnion told me, "I always seek to bring in the speakers that I would want to sit in a room with and learn from. I also am trying to build a solid EM community and push EM forward. I am always trying to bring new docs up to speed in EM with the hope that they will run with it and come back to be one of my teachers."

Topics covered included updates on understanding heavy metal toxicology and treatment (in particular the rare "zebra" elements, by David Quig of Doctor's Data Labs), environmental triggers of autoimmunity, endocrine-disrupting chemicals, and tests to measure and assess initial damage or

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# Retraction

## **Rowen R, Harper D, Robison R. The Antimicrobial Activity of Selected Silver Products. *Townsend Lett.* January 2015;378.**

In the January 2015 issue of the *Townsend Letter*, we published "The Antimicrobial Activity of Selected Silver Products," authored by Robert Rowen, MD; Dennis Harper, DC; and Richard Robison, PhD. After further editorial review, the *Townsend Letter* retracts the publication of this article and the conclusions based on the reported study of silver products. The study cites that one commercial formulation, ACS 200 Extra Strength, had a measurably higher kill rate against MRSA (methicillin-resistant *Staphylococcus aureus*) compared with four other commercial products. Although the laboratory report does not name the other commercial products, unblinded lab data do list the competitor products as pH Structured Silver, Argentyn-23, OxySilver, and ASAP. Three of the aforementioned products were listed as having insignificant "log reduction" killing capacity and reduced percentage kill rate. Reputable independent testing of Argentyn-23 by a commercial laboratory adhering to "good laboratory practices" demonstrated major log reduction killing capacity and percentage kill rate of MRSA.

Inasmuch as the independent testing of Argentyn-23 by a laboratory following compendial procedures as defined by the US Pharmacopeia and the National Formulary guidelines is completely in disagreement with the testing carried out by Robison's university laboratory, the entire study by Rowen, Harper, and Robison is called into question and fails to meet the requirements for journal publication. The paper is hereby

retracted; all references to this article must show that it is officially retracted with the publication of the May 2015 issue of the *Townsend Letter*.

The testing conducted by Robison's laboratory, not a commercial laboratory, was authorized by Rowen and Harper. Robison has previously done laboratory testing for the manufacturer of ACS 200, Results RNA. Robison's analyses for Results RNA include "Antimicrobial Activity of ACS 200 Using *Candida Albicans*" reported in September 2008 and August 2009 and "Antimicrobial Activity of ACS 200 Using *Borrelia Burgdorferi*" reported in September 2009. Natural Immunogenics Corp., the manufacturer of Argentyn 23, was asked by Rowen to participate in a "blinded" study of silver products. Natural Immunogenics declined to participate in the study when it was informed that Robison would be conducting the analysis and that the protocol for testing would not be disclosed. Nevertheless, Rowen and Harper proceeded to test Argentyn 23 without its authorization.

The testing of the five commercial silver products by Robison had serious laboratory methodology flaws. The first concern is that while the testing methodology generally appeared adequate with controls in place, proper neutralization study, and adequate population counts, the lab did not abide by nor list standard testing references. Testing references as required by USP ensure that the methodology used by one laboratory can be understood and replicated by a second laboratory doing identical testing. Proper

commercial microbiology analysis and reporting require references, and Robison's report lacks standard testing references.

Secondly, testing of the kill rate (efficacy) of the silver product was based on a single time point of "2 minutes." Reputable testing of kill rate would require at least 3 or more different time points for analysis. In other words, what is the kill rate at 1 minute, 2 minutes, 3 minutes, and 5 minutes? Is there an appropriate trend with a greater kill rate at 3 minutes compared with 1 minute? Without testing at multiple time points, there would be no conclusive evidence that the product had an effective kill activity that would increase over time. Robison's study based only at a 2-minute measurement lacks the multi-time data needed to confirm product efficacy.

Argentyn 23 has had a compendial study performed by an accredited third-party laboratory following referenced methods that demonstrated at 2 minutes a kill rate for Argentyn 23 of 99.996% with a log reduction of 4.5; this is clearly completely in disagreement with Robison's testing of Argentyn showing a kill rate of 47.1% with a log reduction of 0.28. That there can be such a great disparity between the results questions the validity of Robison's testing of the products. Without such validity and for the other aforementioned concerns, the article is called into question and is hereby retracted.

Jonathan Collin, MD  
Editor-in-Chief  
*Townsend Letter*



## Environmental Medicine

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improvements during treatment. Dr. Patrick presented a moving description of her own experiences living in Paonia, a rural town in southwest Colorado, a one-time paradise that has become ground zero in the battle

winter. I thought that I would collect a pile of CE hours and come home. Since coming back to the office, I've found that the trip changed the way I that practice.



David Quigg, PhD; Lynn Patrick, ND; and Walter Crinnion, ND, at the SpiritMed Environmental Medicine Update in Florida, January 2015

against fracking and its resulting environmental degradation.

This was a problematic conference, as it shined a light on just how much this particular writer doesn't know. Even this brief three-day exposure has left me quite aware that I have a lot to learn in order to help my patients; once one starts looking, it is obvious that many of our patients suffer as a result of environmental toxicants.

I use a simple litmus test to evaluate lecturers or conferences: Do they change the way I view patients when I get back to the clinic? Do I have new tools to use? Not all speakers and certainly not all conference planners appear to understand this. I don't go to conferences to admire pretty presentation slides or near-psychedelic transitions from one slide to the next. I go to conferences to learn things that help patients.

I admit that I initially went to Florida only because I wanted to wet my feet in the ocean and get a break from

Walter Crinnion mentioned that, in his experience, patients with idiopathic thrombocytopenia (ITP) often have elevated solvents in their blood. Since the conference, I've found three patients to test. It's too soon to know if doing so will help my ITP patients; but at least I've got something to offer other than papaya leaves, sesame oil, or whatever the current online fad is.

Last week a 72-year-old-woman who has come to see us off and on for a decade with hypertension returned once more, and it was if I were seeing her anew. Not only does she have high blood pressure (that is poorly controlled with *Rauwolfia* tincture) and asthma (partly controlled with *Ammi visnaga* and a few other herbs), but she's also been recently diagnosed with COPD. Having read one of the preeminent Dr. Wright's excellent books, in which he suggests nebulized glutathione for treating this condition, she arrived for her visit eager to start this treatment. (Special thanks to

Davis Lamson, ND, originator of this therapy, who was kind enough to share not only his directions on how to do it, but also an innovative strategy for doing so at reasonable cost.) My patient also brought in a report from a carotid ultrasound study that had her weepy from fear. Her office visit was different from all prior ones because of Florida; I recognized a common denominator that connected all of her symptomatology.

"How far do you live from that big highway?" I asked her.

"Do you mean the interstate or C-470? We kind of live a few blocks from where they intersect," she replied.

My current theory is that she is sensitive to ultrafine particulates and she is getting more than she can tolerate living close to these highways. Carotid intima thickness (CIMT), the test which had reported that her body was 20 years older than her chronologic age, is often used to assess atherosclerosis. Each standard deviation increase in CIMT increases risk of stroke or myocardial infarction (MI) by about a third. Increases in particulate matter in the air quickly increase CIMT. (Taking statin drugs triples this effect.)<sup>1</sup>

Cardiovascular disease (CVD) is strongly associated with the particulates from motor vehicle exhaust.<sup>2</sup> For women, simply living close to a major roadway increases risk of a sudden death from heart attack by nearly 60%.<sup>3</sup> For people who have suffered a MI, living less than 100 meters from a major roadway is associated with a 27% increase in mortality over a 10-year period.<sup>4</sup>

Changing outdoor air pollution is not something that this patient will be able to accomplish, but she can control indoor air pollution. I was able to convince her to purchase a HEPA air filter and to consider wearing face masks when exposed to extreme levels of pollutants. Using a dust mask can cut levels of inhaled fine particulates by 90%.<sup>5</sup>

A study conducted in Smithers, British Columbia, provides a measure of the impact that using a home air filter has. Smithers has certain peculiarities in topography, which in combination with the high use of wood heat by the

town's inhabitants creates periodic high levels of airborne particulate pollution. Using indoor air filters for just 7 days reduced C-reactive protein levels by almost 33%.<sup>6</sup>

Before the Florida conference, I wouldn't have connected the location of her home with the results of this patient's carotid artery test results. I also wouldn't have had a clue how to monitor her but now I do.

There is a lab test that Dr. Crinnion spoke about several times during the conference. It is a urine test for 8-hydroxy-deoxyguanosine (better known as 8-OH-dG). This chemical is produced when DNA is damaged by reactive oxygen, and testing provides a sensitive quantitative measurement of oxidative stress in the body.

Smoking just two cigarettes is enough to increase baseline levels of 8-OH-dG from 3.3 to 5.1 dG.<sup>7</sup> Levels also rise significantly with exposure to solvent fumes; heavy metals such as mercury, arsenic, cadmium, and lead; and organophosphate pesticides.<sup>8-13</sup> The test is also an excellent reflection of exposure to ultrafine airborne particles produced by motor vehicle exhaust, especially diesel exhaust, making it a valuable measure of the effectiveness of pollution controls and air filtration systems.<sup>14-16</sup> It is also going to be the perfect test to monitor this patient's efforts to get better.

Elevated levels of 8-OH-dG are associated with risk for, or less favorable prognosis in, cancers of the breast, prostate, ovary, lung, nasopharynx, stomach, and bladder.<sup>17-23</sup>

High 8-OH-dG levels are also predictive of CVD, and are positively associated with increasing carotid artery intima media thickness, a marker of atherosclerosis, and with the presence and severity of coronary artery disease.<sup>24</sup> Levels go up after MI and with chronic heart failure; this test provides a measure of disease severity and measures the benefit of therapy.<sup>25-28</sup>

8-OH-dG decreases in response to the therapies that we suggest to patients. For example, simple adherence to a Mediterranean diet appears to lower 8-OH-dG levels.<sup>29</sup>

Aside from a lot of useful tools, only a fraction of which I have space

to mention here, this conference really brought home to me that our days as naturopathic generalists may be numbered. We don't have time in school to learn everything that we need to know. There are certain aspects of practice that our schools do not offer adequate training in; naturopathic oncology is the one that I am most aware of. After attending this conference, I think that environmental medicine is another specialty in which practitioners need advanced training to practice responsibly. If you're interested in diagnosing and treating patients who suffer from environmental toxic exposures, you may not have learned all that you need to know while in school. I certainly didn't. As mentioned earlier, Crinnion and Patrick offer 6-month, 68-credit-hour training programs in environmental medicine. I'm thinking about taking one.

Further information on the programs is available at <http://drcrinnion.com/environmental-medicine-training-for-the-healthcare-professional>.

Videos of the Florida conference are available at <http://www.progressivemedicaleducation.com>.

For more information on the Naturopathic Association of Environmental Medicine, see <http://www.naturopathicenvironment.org>.

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## Shorts

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### Bisphenol A (BPA) and the Heart

Bisphenol A (BPA) may slow electrical conduction in the heart, according to a 2014 laboratory experiment. A known endocrine disruptor, BPA is found in many plastic consumer products, including food and drink containers, water pipes, and medical equipment and tubing. It leaches from these products into food or liquid. Measurable levels have been found in human blood and urine. "Recent epidemiological studies have shown an association between BPA exposure and cardiovascular disease," according to Nikki Gillum Posnack and colleagues at the George Washington University (Washington, DC).

In their study, Posnack and colleagues exposed whole hearts, taken from adult female Sprague-Dawley rats, to various concentrations of BPA (0.1  $\mu\text{M}$ , 1  $\mu\text{M}$ , 10  $\mu\text{M}$ , 25  $\mu\text{M}$ , 50  $\mu\text{M}$ , 100  $\mu\text{M}$ ) for just 15 minutes. Each heart served as its own control. The researchers measured atrial and ventricular activation times during sinus and paced rhythms and then calculated atrioventricular activation intervals and epicardial conduction velocities. Reduced ventricular conduction velocity and prolonged PR segment appeared first, at just 0.1  $\mu\text{M}$  BPA – well below reported human urinary concentrations of 0.024 to 8.5  $\mu\text{M}$  BPA. (PR segment is the interval between the onsets of atrial depolarization and ventricular depolarization.) Prolonged action potential duration (amount of time that voltage remains above threshold) first occurred at 1  $\mu\text{M}$  BPA, and delayed atrioventricular conduction appeared at 10  $\mu\text{M}$  BPA. The highest tested concentration (100  $\mu\text{M}$  BPA) produced complete heart block.

The mechanisms underlying BPA's effect on cardiac electrical conduction are unknown. This and earlier *in vitro* studies indicate that BPA may alter ionic currents in nodal cells. Posnack et al. say, "If BPA induces ion channel alterations in atrial tissue, exposure will likely affect ion channels in other tissue compartments."

Recent consumer concerns about BPA safety have pushed manufacturers to produce BPA-free containers. Unfortunately, BPA-free plastics also leach synthetic

estrogens – some of which are as hazardous or worse, according to J. Bilbrey at *Scientific American*. The precautionary principle suggests that patients with heart conduction abnormalities avoid plastics as much as possible.

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### Disordered Sleep and Heart Disease

Postmenopausal women with a history of insomnia and habitual sleep duration of 10 hours or more each night are more likely to develop heart disease than those with normal sleep patterns, according to a 2013 study led by Megan Sands-Lincoln, PhD. The study involved 86,329 women, aged 50 to 79 years, who completed the validated WHI Insomnia Rating Scale and reported on their typical sleep duration as part of the Women's Health Initiative Observational Study. Demographic information and lifestyle risk factors were also collected. None of the women included in the final analysis had coronary heart disease (CHD) or cardiovascular disease (CVD) at baseline. The primary end point was incident CHD and CVD, which included myocardial infarction, hospitalized angina, coronary revascularization, ischemic stroke, and CHD death.

The researchers found 5359 cases of incident CHD during 881,888 person-years of follow-up and 7257 cases of incident CVD with 867,513 person-years. (The difference in person-years reflects cohort-size of CHD-free or CVD-free women at baseline.) Short ( $\leq 5$  hours) and long ( $\geq 10$  hours) sleep durations were associated with an increase in CHD and CVD, but the increase was not significant when age, race, and risk factors (e.g., BMI, smoking, physical activity, etc.) were taken into account. However, CHD risk and CVD risk were significantly greater in women with high insomnia scores (WHIIRS  $\geq 9$  out of a possible 20) at baseline even after adjusting covariates.

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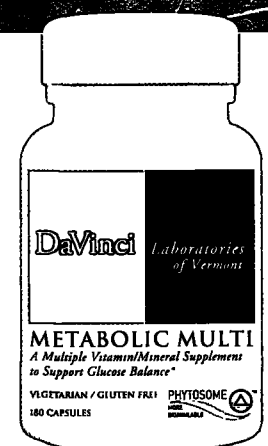
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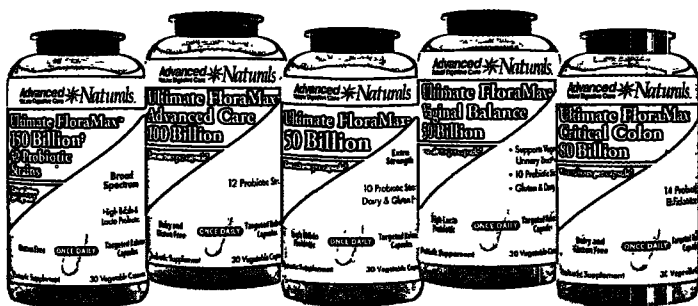
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► continued from page 18

The combination of long sleep duration and a high level of insomnia was associated with the greatest CHD and CVD risks. Women with insomnia who reported sleeping  $\geq 10$  hours had “almost double the risk of incident CHD” (hazard ratio = 1.93) and increased risk (HR = 1.76) of CVD compared with those who reported midrange sleep (7 to 8 hours). Interestingly, insomnia level did not increase CHD and CVD risk in women reporting midrange sleep duration. Women with high insomnia scores who slept 7 to 8 hours had about the same risk of having a cardiovascular event as those with the same sleep duration and low insomnia scores.

The authors did consider the impact of sleeping pill use in their analysis. They report that an earlier study, conducted by A. Hartz and J. J. Ross, found a significant association between hypnotic use and mortality in postmenopausal women. (Oddly, this study also found a “substantial elevated risk for melanoma” in sleeping pill users.) Although Sands-Lincoln et al. observed no correlation between sleeping pill use and heart disease in their study, they say that “nondifferential misclassification could have biased these results. ...” In their opinion, the effect of hypnotic drugs on cardiovascular outcomes needs further investigation.

This study does not show cause and effect, only correlations. In addition, the observations should not be generalized to populations other than postmenopausal women. Still, the association between longer (but not shorter) sleep duration, sleep quality, and adverse cardiovascular events raises questions about underlying biological processes that deserve investigation.

Hartz A, Ross JJ. Cohort study of the association of hypnotic use with mortality in postmenopausal women. *BMJ Open*. 2012; 2(5):e001413. Available at [www.ncbi.nlm.nih.gov/pmc/articles/PMC3467595](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3467595). Accessed February 27, 2015.

Sands-Lincoln M, Loucks EB, Lu B, et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative. *J Womens Health*. 2013; 22(6):477-485. Available at [www.ncbi.nlm.nih.gov/pmc/articles/PMC3678565](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3678565). Accessed February 27, 2015.

### Fish Oil-Based Drug for Vascular Scarring

In 1 out of 4 cases, vascular scar tissue that forms after angioplasty, bypass surgery, and stent placement narrows the vessel, effectively creating another blockage. The failure rate for leg artery stents or angioplasty is even higher – as much as 40% to 50% in one year, according to Michael S. Conte, MD, chief of Vascular & Endovascular Surgery at University of California-San Francisco (UCSF). Researchers at UCSF are investigating a fish oil-based drug that lessens blood vessel scarring and appears to accelerate healing.

A UCSF Bioengineering and Therapeutic Sciences research team, led by Tejal Desai, PhD, is testing two methods for delivering the drug to the traumatized area. The first

method consists of a tiny, biodegradable, drug-containing film that gets placed around the vessel at its point of injury. The drug is gradually absorbed through the vessel wall. The researchers are also investigating stents with textured surfaces, consisting of minute tubular structures. These nanotubes can hold the drug and gradually release it into the body.

“Excessive inflammation is a problem throughout the field of surgery,” says Conte. Delivering nontoxic, anti-inflammatory compounds directly to damaged areas may improve cardiovascular and surgical outcomes.

New drugs from fish oil could aid artery repair [online article]. November 24, 2014 UCSF. Available at <http://medicalxpress.com/news/2014-11-drugs-fish-oil-aid-artery.html>. Accessed January 27, 2015

### Phellinus Linteus and Cancer

*Phellinus linteus* (sang hwang, meshimakobu; PL), a hoof-shaped mushroom that grows on old mulberry trees, is revered in Asia for its ability to promote longevity and enhance life energy (qi). Traditionally, it has been used for centuries to prevent and treat gastroenteric disorders, diarrhea, hemorrhage, cancer, and other illnesses. Western researchers are most attracted to its anticancer effects. In vitro experiments with human cancer cell lines and in vivo animal studies show that PL may be useful for treating and preventing several types of cancer.

In a 2008 study, D. Sliva and colleagues used an aqueous solution of PL (Mushroom Wisdom Inc.) to investigate the mushroom's effect on a highly invasive human breast cancer cell line (MDA-MB-231). Although PL (1.0 mg ml<sup>-1</sup>) killed only 13.5% of the cells after 72 hours, it suppressed its spread by 86.6%, compared with control. PL inhibited cancer cell adhesion, migration, and invasion, thereby inhibiting proliferation and colony formation. PL also suppressed angiogenesis.

Instead of using the whole mushroom, Sensuke Konno and colleagues at New York Medical College have focused on two fractions (bioactive extracts): PL-ES and PL-I-ES. In their 2015 study, they tested the fractions on 10 human cancer cell lines: prostate cancer metastasized to bone,

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prostate cancer metastasized to brain, prostate cancer metastasized to lymph node, bladder cancer, kidney cancer, lung cancer, breast cancer, stomach cancer, liver cancer, and brain cancer. "PL-ES (100  $\mu\text{g}/\text{mL}$ ) exhibited potent anticancer activity, resulting in a significant (40-80%) growth reduction in all 10 cancer cells at 72 hours," the authors report. Only the liver, breast cancer, stomach, and prostate-metastasized-to-bone cancers responded to PL-I-ES (100  $\mu\text{g}/\text{mL}$ ). At 250  $\mu\text{g}/\text{mL}$ , PL-I-ES, reduced growth in all cell lines except for kidney, prostate metastasized to brain, and prostate metastasized to lymph node. The researchers look for synergistic effects by testing the two fractions together.

Konno and colleagues found that the fractions' effectiveness correlated to activation of Csp-3 and Csp-9, enzymes in cancer cells that regulate apoptosis (cell death). The cancers that had the least growth after exposure to PL-ES and PL-I-ES showed Csp-3/9 activation, which produces cancer-killing oxidative stress. The authors point out that "cancer cells have been shown to be more vulnerable to free radicals than normal cells." An animal study to assess the fractions' safety, efficacy, and possible adverse effects is in progress, according to Konno et al. Although the whole mushroom has been used safely for generations in Asian medicine, isolated fractions may have unexpected effects.

Konno S, Chu K, Feuer N, Phillips J, Choudhury M. Potent anticancer effects of bioactive mushroom extracts (*Phellinus linteus*) on a variety of human cancer cells. *J Clin Med Res*. 2015;7(2):76-82. Available at [www.ncbi.nlm.nih.gov/pmc/articles/PMC4245057/pdf/joc](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4245057/pdf/joc). March 5, 2015.

*Phellinus linteus*, Mesima, Meshmakobu, Song-gen [Web page] Medical Mushrooms.net. [www.medicalmushrooms.net/phellinus-linteus](http://www.medicalmushrooms.net/phellinus-linteus). Accessed March 8, 2015.

Sliwa D, Jedinak A, Kawasaki J, Harvey K, Slivova V. *Phellinus linteus* suppresses growth, angiogenesis and invasive behaviour of breast cancer cells through the inhibition of AKT signaling. *Br J Cancer*. 2008;98(8):1348-1356. Available at <http://www.nature.com/bjcl/journal/v98/n8/full/6604319a.html>. Accessed March 5, 2015.

*Phellinus linteus* [online article] Thai-Korea Natural *Phellinus* Mushroom Research Center. [www.phellinus-research.com/en/phellinus-linteus](http://www.phellinus-research.com/en/phellinus-linteus). Accessed March 8, 2015.

### Slow Breathing and Heart Rate Variability

During slow, deep breathing, blood pressure decreases and heart rate variability (HRV) increases. HRV reflects cardiac autonomic inputs and is a measure of cardiovascular health. Low HRV indicates impaired autonomic control and is characteristic of hypertension, myocardial infarction, diabetes, and congestive heart failure. In people with essential hypertension, breathing 6 breaths per minute improves arterial baroreflex sensitivity (BRS) and lowers blood pressure. The same respiration rate improves BRS and oxygen saturation in people with chronic heart failure and decreases sympathoexcitation in those with COPD. However, maintaining that slow breath rate throughout the day is virtually impossible, and the improvements recede when slow breathing ends. Can regular practice of slow breathing have a residual effect on HRV and cardiovascular health? Two recent studies indicate that it does.

Swarnalatha Nagarajan at Karuna Medical College (Palakkad, Kerala, India) led a small study with 8 healthy participants and 6 matched young adult controls. The participants performed a half hour of slow breathing

(4-second inhalation and 6-second exhalation), using verbal prompts on audio CDs for 4 weeks. The controls followed their normal routines. When comparing results with baseline measures, Nagarajan's research team observed a significant increase in the breathing group's HRV and decrease in their respiration rate and mean arterial pressure during quiet standing – despite the small number of participants. (Small sample size increases the probability of false negative results.) Nagarajan says that larger studies might also show a significant reduction in mean heart rate.

A 2014 study, led by Gopal Krushna Pal (Pondicherry, India), focused on a different aspect of breathing: the effect of left-nostril breathing vs. right-nostril breathing on HRV and cardiovascular function. This study involved 85 healthy medical students who were divided into three groups: right-nostril breathers (RNB;  $n = 30$ ), left-nostril breathers (LNB;  $n = 30$ ), and controls who engaged in no breathing practice ( $n = 25$ ). Participants in the active groups were instructed to inhale and exhale on counts of 5 each (i.e., 6 breaths per minute) for 1 hour each day while pressing either the left or right nostril closed. At baseline and at the end of 6 weeks, researchers measured participants' heart rate variability, basal heart rate, and blood pressure (systolic and diastolic). Mean arterial pressure (MAP) was also calculated.

Compared with baseline, left-nostril breathers showed a significant decrease in heart rate, blood pressure, and MAP and improvement in HRV indices, reflecting improvement in vagal tone and increased parasympathetic activity, say the authors. In contrast, the right-nostril breathers showed a significant increase in the cardiovascular measurements and decline in HRV, indicating greater sympathetic activity and poorer vagal cardiovascular modulation. The control group's cardiovascular measurements and HRV indices did not significantly change from baseline. The results caused the authors to warn students against right-nostril breathing practices, which appear to increase cardiovascular stress.

Pal et al. note that persistent unilateral nasal obstruction has been "associated with a number of chronic disorders that occur due to [sympathovagal imbalance] such as migraine, hyperthyroidism, asthma, and cardiac dysfunctions." They suggest that intentional, slow, unilateral nasal breathing may provide a solution to autonomic dysregulation.

Nagarajan S. Effect of slow breathing training for a month on blood pressure and heart rate variability in healthy subjects. *Nat J Physiol Pharm Pharmacol*. 2014;4(3):245-248. Available at [www.scopemed.org/fulltextpdf.php?mno=158790](http://www.scopemed.org/fulltextpdf.php?mno=158790). Accessed January 28, 2015.

Pal GK, Agarwal A, Karthik S, Pal P, Nanda N. Slow yogic breathing through right and left nostril influences sympathovagal balance, heart rate variability, and cardiovascular risks in young adults. *N Am J Med Sci*. March 2014;6(3):145-151. Available at [www.ncbi.nlm.nih.gov/pmc/articles/PMC3978938](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3978938). Accessed January 28, 2015

### Triglyceride Levels and Chronic Heart Failure

A low serum triglyceride level in female patients with chronic heart failure (CHF) is associated with an increased risk of cardiac death, according to a 2013 study. Triglyceride, a simple fat compound, is an important source of stored energy. Guliz Kozdag, MD, and colleagues hypothesized that low triglyceride levels would predict a greater mortality risk among CHF patients.

To test their hypothesis, the Turkish research team evaluated 637 patients (409 men and 228 women) who



were hospitalized for worsening heart failure from January 2003 through December 2009, and followed them by phone and periodic outpatient exams for a mean duration of  $38 \pm 15$  months (range, 3–82 mo). Cardiac death was the study's primary end point.

Surviving patients, regardless of sex, had higher triglyceride levels at baseline than nonsurviving patients. Surviving women had triglyceride levels of  $147 \pm 70$  mg/dL, compared with  $119 \pm 62$  mg/dL for those who died ( $p = 0.001$ ). The difference between surviving and nonsurviving men was less pronounced:  $130 \pm 74$  mg/dL vs.  $116 \pm 57$  mg/dL ( $p = 0.038$ ).

Cox regression analysis showed that a low triglyceride level was an independent predictor of cardiac death only in women. Left ventricular ejection fraction  $< 0.145$  (Hazard ratio = 3.208), sodium levels  $< 128.5$  mEq/L (HR = 2.674), and older age (HR = 1.057) were the most significant predictors in men. For women, however, NYHA functional class (HR = 2.002) and triglyceride level below 150 mg/dL (HR = 1.995), and a history of coronary artery disease (HR = 1.608) were the significant independent predictors of cardiac death. The authors say, "The ROC curves showed that the best cutoff value for predicting cardiovascular death in women was a triglyceride level of  $< 70.5$  mg/dL (79% sensitivity and 91% specificity)."

Low triglyceride levels are likely a consequence of decreased food intake, increased inflammation, cachexia, and/or liver congestion – all of which are associated with chronic heart failure progression.

Kozdag G, Ertas, G, Emre E, et al. Low Serum triglyceride levels as predictors of cardiac death in heart failure patients. *Tex Heart Inst J*. 2013. Available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853839>. Accessed February 3, 2015.

### Yoga and Heart Disease

Yoga improves cardiovascular and metabolic risk factors, according to a 2014 systematic review and meta-analysis article. The combination of stretching and controlled breathing, characteristic of commonly practiced hatha yoga, is believed "to stabilize the hypothalamic-pituitary-adrenal axis and sympathoadrenal activity," according to Paula Chu at Harvard University and colleagues. Their 2014 systematic review indicates that yoga's effect on cardiovascular health is comparable to more aerobic exercise.

The researchers conducted electronic searches of multiple databases and located 37 randomized controlled trials (RCTs) for the systematic review and 32 RCTs for the meta-analysis. The studies, published in English before January 2014, were peer reviewed and reported cardiovascular and metabolic risk factors as outcomes. Some RCTs used nonexercise controls such as usual medical care, a waiting list/no intervention, relaxation, diet alone, or cognitive-based therapy. Other studies compared yoga with aerobic exercise (e.g., physical training, aerobic exercise, cycling, running, brisk walking). Chu and colleagues analyzed the studies with exercise controls separately from those with nonexercise controls.

Compared with nonexercise controls, yoga significantly improved each of the primary outcomes: body mass index, systolic blood pressure, low-density lipoprotein cholesterol,

and high-density lipoprotein cholesterol. In addition, most secondary outcomes – body weight, diastolic blood pressure, total cholesterol triglycerides, heart rate, and smoking status – improved significantly in the yoga group compared with nonexercise controls. Only fasting blood glucose and glycosylated hemoglobin did not.

When yoga practice was compared with aerobic exercise, Chu et al. were surprised to find that improvements in primary and secondary outcomes were about the same. "The similarity in effectiveness on risk factors between the two forms of exercise suggest that there could be comparable working mechanisms, with some possible physiological aerobic benefits occurring with yoga practice, and some stress-reducing, relaxation effect occurring with aerobic exercise," say the authors.

More well-designed studies with longer follow-up are needed to determine the most beneficial type(s) of yoga, the optimal practice length, and whether yoga actually prevents cardiovascular events and mortality. Still, this review indicates that traditional aerobic exercise is not the only activity that reduces cardiovascular risk – which is great news for those who enjoy yoga.

Chu P, Gotink RA, Yeh GY, Goldie SJ, Hunink MGM. The effectiveness of yoga in modifying risk factors for cardiovascular disease and metabolic syndrome: A systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. December 15, 2014. Available at [www.researchgate.net](http://www.researchgate.net). Accessed March 1, 2015.

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# War on Cancer

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## Cancer and Its Strange Metabolism

One of the key characteristics of cancer is abnormal metabolism.

A normal human cell takes in glucose (i.e., sugar) as its main fuel source and, through a very efficient mechanism, turns each glucose molecule into as many as 36 packets of ATP energy (Rich 2003). This method is called oxidative phosphorylation (OxPhos, for short), which takes place in specialized bodies within each cell called the mitochondria. But cancer cells typically have lost half their mitochondria and, therefore, much of their ability to perform this trick. They must rely on a primitive and relatively inefficient method of energy generation: fermentation. In this method, the cell turns one molecule of glucose into just two packets of ATP energy. A byproduct of fermentation is lactic acid. So, basically, cancer cells ferment, utilizing the same process that turns milk into yogurt, or grape juice into wine.

Through the work of the great German biochemist Otto Warburg, MD, and other scientists, such as Peter Pedersen, PhD, of Johns Hopkins School of Medicine, we now know a great deal about how and why cancer cells rely on fermentation for their energy needs. For instance, a normal cell typically has 200 or so mitochondria. But cancer cells typically have lost half of these, and therefore make up for this mitochondrial deficiency through fermentation. Given the fact that cancers often replicate quickly, their avidity for glucose is a defining characteristic of most tumors.

Proof of this is the accuracy of positron emission tomography (PET) scans. In a PET scan, a patient is injected with a radioactive form of glucose, called FDG. About an hour later, doctors scan the body, looking for signs of radioactivity. Areas of brightness on the scan indicate where glucose is being taken up in greater than normal amounts. Generally speaking, areas that light up coincide with primary tumors or metastatic growths. The more a tumor glows on the PET scan, the more "avid" it is for glucose, and the more malignant it is likely to be. The PET scan thus both utilizes the so-called Warburg effect and is its most dramatic proof of principle.

Since cancer is typically associated with this heightened

consumption of glucose (a process that Warburg called "aerobic glycolysis"), there should be a way to decrease its supply of sugar and thereby slow or halt its growth. Over the years, several ways have been suggested. Pharmaceutical companies are also at work on a number of compounds that block the uptake of glucose by tumors. But a simple self-help strategy comes to mind: one could reduce one's overall intake of food. This is partial or complete fasting. Another more focused method involves the consumption of few carbohydrates, the ultimate source of most of the glucose that circulates in our bloodstream. One can even consume so few carbohydrates that the body then switches to burning fatty acids for energy. This state is called *ketosis*, and the regimen in question the "ketogenic diet."

Dietary restriction, intermittent fasting and the ketogenic diet have all been explored as means of controlling the growth of cancer since the 1920s. But since the publication of Prof. Thomas Seyfried's *Cancer As A Metabolic Disease* (2012), this method has become increasingly popular among cancer patients. At the same time, it has come under furious attack from some doctors and scientists, on both theoretical and practical grounds. Often these arguments are tinged with intense emotion. People become attached to their own dietary regimens and resent any attempts to change them.

But, emotion aside, the key question is, what does the science show on the efficacy of this approach?

In December 2014, the prestigious online journal *PLOS One* published a systematic review and meta-analysis of the best studies of the past 20 years that have evaluated dietary restriction regimens for cancer such as caloric restriction, the ketogenic diet, and intermittent fasting (Lv 2014). The authors come from the University of Nanjing, China. They reviewed a total of 1463 articles and winnowed this down to 157 papers for detailed review. In the end, 59 animal studies fulfilled all of their rigorous inclusion criteria. This selection yields a comprehensive overview of the state of the science. We are thus in a much better position to evaluate the merit of dietary strategies, at least from the point of view of laboratory science.

The authors' bottom-line conclusion was as follows: "About 90.9% of the relevant studies showed that caloric restriction plays an anti-cancer role."

The ketogenic diet was also effective. Intermittent fasting was beneficial, but not as significant at preventing cancer as going into ketosis and limiting the number of calories.

The authors conclude: "Caloric restriction and ketogenic diet are effective against cancer in animal experiments while the role of intermittent fasting is doubtful and still needs exploration. More clinical experiments are needed and more suitable patterns for humans should be investigated."

#### *Caloric Restriction*

In 1909, C. Moreschi made the first observation that calorie-restricted diets led to a decrease in tumor growth. (All that I could find about Moreschi was that he or she was a colleague of Prof. Paul Ehrlich of the Royal Prussian Institute for Experimental Therapeutics in Frankfurt-am-Main, Germany.) The great Peyton Rous, who later won the Nobel Prize for his work on viruses, pursued the topic at the Rockefeller Institute. Kanematsu Sugiura, DSc, of Sloan-Kettering Institute, New York, experimented with calorie-restricted diets in the 1920s. As David Kritchevsky, PhD, of the Wistar Institute, Philadelphia, wrote: "Sugiura and Benedict (1926) found that after excision of spontaneous tumors there was 82 percent recurrence in fully fed mice but only 27 percent recurrence in underfed mice" (2002).

That was a 55% difference in recurrences. Yet this finding also fell by the wayside. Sugiura told me in 1974 that this was because cancer doctors of the time recoiled at the idea of "starving" their patients, due to a fear of initiating or exacerbating cancer cachexia, the wasting syndrome.

Experiments with calorie restriction did not resume until the work of Albert Tannenbaum and Carl A. Baumann in the 1940s and then skipped another few decades. More recently, it has come into vogue, after it was found that "energy restriction enhances DNA repair and moderates oxidative damage to DNA. Energy restriction reduces oncogene expression as well" (Kritchevsky 2001).

In the Nanjing study, the most frequently studied cancer types were mammary (breast), prostate, brain, pancreatic, and hepatic cancers, but skin, colorectal and ovarian cancers were also sometimes investigated. Forty of the 44 relevant studies (90.9%) "supported the positive anticancer role" of calorie restriction.

It is more than coincidental that many religious and philosophical systems have specified periodic fasts throughout the calendar year. In Judaism, although Yom Kippur is the best known, there are seven fast days in the calendar. One thinks of Lent in the Catholic tradition and Ramadan in Islam. Could it be that these ancient traditions found their way to this concept because of health reasons, as well as religious penance?

#### *Ketogenic Diet*

A ketogenic diet is one in which carbohydrates are so restricted that the person fulfills his or her energy requirements through the metabolism of ketone bodies. There is a great deal of mythology surrounding the topic of ketogenesis. The most prevalent confusion, which obscures many discussions of the

topic, is that between ketosis and ketoacidosis. The latter is a very dangerous production of huge amounts of highly acidic ketones, generally seen in uncontrolled type 1 diabetics. Ordinary ketosis, such as that attained in a carbohydrate-restricted diet, is a common and normal condition seen during periods of fasting, including sometimes even during one's normal overnight fast. Since the 1970s, followers of the diet doctor Robert Atkins, MD, have used ketosis as a way to rapidly lose excessive weight.

According to the Chinese authors, there have been nine high-quality studies in mice of ketone-inducing carbohydrate restriction and cancer. The tumor types included primary prostate, brain, colon, and stomach, as well as metastatic cancers.

Eight of the nine studies (88.9%) supported that carbohydrate restriction is protective [in] cancer," said the authors of their recent meta-analysis.

The amount of carbohydrates in these experiments ranged from 0% to 20% of the diet. A "nutritionally complete and commercially available ketogenic diet" was also studied, and yielded positive results as well. In humans, a diet of approximately 25 to 30 grams of carbohydrate per day will put one into ketosis.

#### *Intermittent Fasting (IF)*

There are eight high-quality studies on intermittent fasting and cancer. Five of these (62.5%) reported positive conclusion.



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# War on Cancer



Three studies investigated the role of IF on initiation of cancer, and two of them showed the effectiveness of IF.

## Meta-Analysis

The authors also combined the results of 22 studies, 21 of which involved calorie restriction. The pooled effect of calorie restriction was a relative risk of cancer of 0.20. This means that animals that were put on calorie restriction had only one-fifth the incidence of cancer as mice eating as much as they wanted (*ad libitum*). These results were statistically significant. Here are two of the most dramatic findings.

**Von Tungeln Study.** Dr. Linda S. von Tungeln and colleagues at the National Center performed the first study in 1996 for Toxicological Research, Jefferson, Arkansas. The mice in question were given one of two carcinogens.

While between 33% to 50% of the mice on an ordinary *ad libitum* diet developed liver nodules, including cancers, there were no hepatic nodules in similarly treated mice on a calorie-restricted diet.

Von Tungeln concluded: "Over-nutrition could be an important factor in human diet-related cancer."

**Blando Study.** Another study is from Jorge Blando et al., of the University of Texas M. D. Anderson Cancer Center (2011). Mice that were predisposed to develop prostate cancer were placed on a 30% calorie-restricted diet and then compared with overweight controls and obese animals.

Thirty percent caloric restriction (CR) "significantly reduced the incidence of *in situ* adenocarcinomas" at 6 months compared with both the overweight and diet-induced obesity regimen animals. The 30% caloric reduction "significantly delays prostate cancer progression. ..."

This paper contains another astonishing finding: "Notably, 30% CR completely suppressed the formation of invasive adenocarcinomas at both 3 and 6 months. ..."

That's right – there was no invasive prostate cancer in the group that had their calories restricted by 30%. But obesity was also associated with a more aggressive tumor: "[A]t 6 months of age, both the overweight control and diet-induced obesity (DIO) groups had poorly differentiated adenocarcinomas, with a significantly greater incidence observed in the DIO diet group compared to the overweight control diet group."

Lately, there is renewed interest in calorie restricted or ketogenic diets in human cancer, mostly as a result of Pedersen's work at Johns Hopkins and Seyfried's outstanding book. There has also been a persistent drumbeat of statements that ketosis is harmful and could even accelerate tumor growth (Bonuccelli 2010). I cannot address these concerns in detail in this column. However, my overall perception is that if it were true that ketosis is harmful in the context of cancer, then one would expect to see that demonstrated in the many high-quality studies reviewed in the recent meta-analysis, and especially in the nine papers that specifically evaluated the ketogenic diet. Instead, as shown, eight of those nine ketosis studies supported the idea that carbohydrate restriction was

highly protective against cancer. This concept is currently being subjected to clinical trials.

It is even more true today, as it was a decade ago, that "... the use of the ketogenic diet internationally has increased dramatically" (Kossoff 2005).

Overall, the ketogenic diet remains a highly promising strategy for diminishing the growth and aggressiveness of cancer. But, overall, I would say there is very little enthusiasm in our profit-driven medical system for researching simple dietary approaches.

## The World Turned Upside Down: A Brief Book Review

I would also call the reader's attention to a new book available online through print and e-reader called *The World Turned Upside Down*, by Richard David Feinman, PhD. Feinman is professor of cell biology at the SUNY Downstate Medical Center in Brooklyn, where he has been teaching for over 40 years. He is the former coeditor-in-chief of the journal *Nutrition and Metabolism* and has organized various conferences on the nutritional and metabolic aspects of carbohydrate restriction. He is the author of 77 PubMed-listed publications, dating to 1977. I think it is fair to say that he is a reliable guide to the intricacies of carbohydrate restriction and ketogenesis as it relates to such topics as weight loss, diabetes, and cancer. But this is no dry textbook. Feinman intersperses personal anecdotes among his scientific explanations. The result is a highly accessible, thoroughly enjoyable review of the "second low-carbohydrate revolution." (The first such revolution was that of Robert C. Atkins, MD, at the end of the 20th century.) Carbohydrate restriction on the part of a considerable portion of the population (think of the 86 million Americans with prediabetes alone!) has major implications not just for health and medicine, but for economics as well. It is no exaggeration to call this a "revolution" in thinking and practice.

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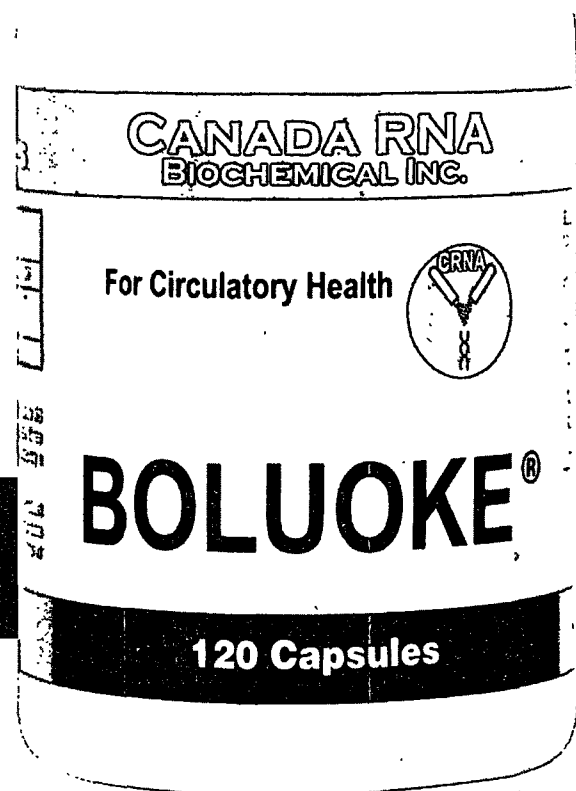
Ralph W. Moss, PhD, is the author of 12 books on cancer-related topics. The former science writer at Memorial Sloan-Kettering Cancer Center, for 35 years Moss has investigated the validity of many cancer treatments. He currently directs the *Moss Reports*, a library of reports for patients on over 200 different cancer diagnoses. ◆

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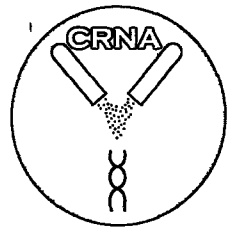
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# Literature Review & Commentary

by Alan R. Gaby, MD  
drgaby@earthlink.net

## Intravenous Iron for Heart Failure Patients

Three hundred four patients (mean age, 69 years) with symptomatic heart failure (left ventricular ejection fraction of 45% or lower) and iron deficiency (defined as serum ferritin less than 100 ng/ml, or 100 to 300 ng/ml if transferrin saturation was less than 20%) were randomly assigned to receive, in double-blind fashion, intravenous iron (as ferric carboxymaltose) or placebo (saline) over a 52-week period. Iron was given at a dosage and frequency based on body weight and initial hemoglobin level, with the aim of correcting iron deficiency and subsequently maintaining iron sufficiency. Compared with placebo, iron supplementation resulted in sustained improvement in functional capacity, symptoms, and quality of life. These differences were statistically significant from week 24 until the end of the study. The frequency of hospitalization for worsening heart failure was significantly lower by 61% in the iron group than in the placebo group ( $p < 0.01$ ). The death rate was nonsignificantly lower by 14% in the iron group than in the placebo group.

**Comment:** In addition to its role in hemoglobin synthesis, iron is a cofactor for some of the enzymes of the electron-transport chain, which are essential for myocardial energy production. Iron deficiency is common in patients with heart failure, and is a strong predictor of unfavorable outcomes, including increased mortality. Previous research has shown that intravenous administration of iron improves functional capacity in iron-deficient heart failure patients. The beneficial effect of iron was similar in patients with and without anemia. These positive effects of intravenous iron were confirmed in the present study.

While intravenous iron has occasionally caused anaphylactic reactions, this side effect became rare after high-molecular-weight iron dextran was largely replaced by newer intravenous iron preparations. Malabsorption is common in patients with heart failure, and it is not always possible to correct iron deficiency in these patients with oral iron

supplements. Therefore, intravenous iron treatment should be considered in selected cases.

Ponikowski P et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. Epub 2014 Aug 31

## Vitamin D Treatment of Heart Failure

Twenty-three patients (mean age, 74 years) with chronic heart failure and a 25-hydroxyvitamin D (25[OH]D) level less than 30 ng/ml (mean, 17.4 ng/ml) were randomly assigned to receive, in double-blind fashion, vitamin D3 or placebo. The dosage of vitamin D was 600,000 IU orally at the start of the study, then 100,000 IU at weeks 10 and 20 (total dose, 800,000 IU). In the vitamin D group, the mean left ventricular ejection fraction (LVEF) increased from 39.1% at baseline to 47.2% after 25 weeks. In the placebo group, the mean LVEF decreased from 43.6% at baseline to 39.4% after 25 weeks. At 25 weeks, the mean LVEF was significantly higher in the vitamin D group than in the placebo group ( $p < 0.05$ ).

In a second study, 64 patients (mean age, 66 years) with chronic heart failure (New York Heart Association class II or III) and a serum 25[OH]D level of 37.5 ng/ml or lower (mean, 19.1 ng/ml in the vitamin D group, 17.8 ng/ml in the placebo group) were randomly assigned to receive, in double-blind fashion, 50,000 IU of vitamin D3 once a week or placebo for 6 months. All patients received 400 mg of calcium citrate twice a day. Compared with placebo, vitamin D had no significant effect on maximal oxygen consumption, 6-minute walking distance, isokinetic muscle strength, or the timed get-up-and-go test.

**Comment:** These 2 studies of vitamin D supplementation in patients with chronic heart failure produced conflicting results. In the first study, vitamin D supplementation improved cardiac function, as measured by LVEF. In the second study, vitamin D supplementation failed to improve various measures of cardiac function and physical performance, although LVEF was not measured. The discrepant results cannot be explained by

differences in baseline vitamin D status, since both groups had similarly low serum 25(OH)D levels. Possible explanations for the conflicting findings are the difference in age between study groups (older people might benefit more than younger people from vitamin D supplementation) and the different outcome measures used in the 2 studies. Another difference is that the mean dose was lower (about 4500 IU per day) in the study in which vitamin D was beneficial than in the study in which it was not beneficial (about 7100 IU per day). In previous columns, I have cited evidence that high doses of vitamin D are sometimes less effective than more moderate doses in the treatment of conditions such as osteoporosis (see below) and multiple sclerosis. It is possible that 7100 IU per day is above the "therapeutic window" for vitamin D in the treatment of heart failure. Further research is needed to determine what types of patients are most likely to benefit from vitamin D supplementation, and what the optimal dosage range is.

Dalbeni A et al. Effects of six months of vitamin D supplementation in patients with heart failure: A randomized double-blind controlled trial. *Nutr Metab Cardiovasc Dis.* 2014;24:861-868.  
 Boxer RS et al. A randomized controlled trial of high dose vitamin D3 in patients with heart failure. *JACC Heart Fail.* 2013;1:84-90.

### Vitamin D for Heart Failure Prevention

In a double-blind trial, 5292 people aged 70 years or older (mean age, 77 years; 85% female) with a history of a low-trauma fracture were randomly assigned to receive 800 IU per day of vitamin D, 1000 mg per day of calcium, vitamin D plus calcium, or placebo for 24 to 62 months. Cardiovascular events (one of the prespecified end points) were recorded during the supplementation period and for an additional 3 years after the supplementation period. Compared with no

vitamin D, vitamin D supplementation significantly decreased the incidence of heart failure by 25%, but had no significant effect on the incidence of myocardial infarction or stroke.

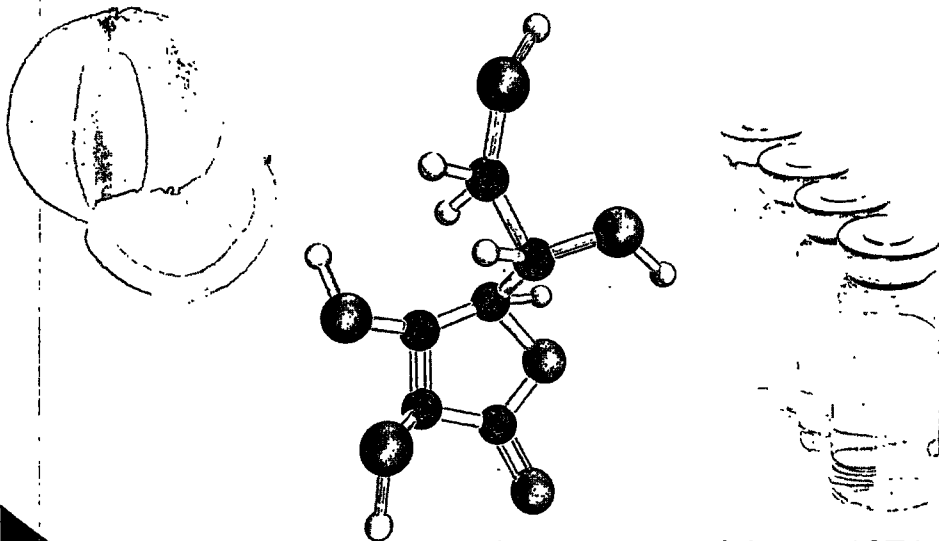
**Comment:** This study found that supplementation with 800 IU per day of vitamin D reduced the incidence of heart failure by 25% in patients with a history of osteoporotic fractures. It is noteworthy that a clear benefit was seen with a relatively modest dose of vitamin D. Whether higher doses would be more effective or less effective for heart failure prevention has not been investigated; however, circumstantial evidence suggests that vitamin D may lose some of its efficacy with excessive dosing.

Ford JA et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr.* 2014;100:746-755.

### Olive Oil Prevents Atrial Fibrillation

In the PREDIMED (Prevencion con Dieta Mediterranea) trial, 7447 Spanish individuals (aged 55-80 years) who were at high risk of developing cardiovascular disease but who had no cardiovascular disease at baseline were randomly assigned to 1 of 3 diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). A previously published analysis (Estruch R et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med.* 2013;368:1279-1290) found that the Mediterranean diet enriched with either extra-virgin olive oil or mixed nuts reduced the incidence of the composite end point of stroke, myocardial infarction, and cardiovascular mortality. In the present post hoc analysis, among 6705 participants without

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atrial fibrillation at baseline, after median follow-up period of 4.7 years, compared with the control diet, the Mediterranean diet with extra-virgin olive oil significantly reduced the risk of atrial fibrillation by 38%, and the Mediterranean diet with nuts nonsignificantly decreased the incidence of atrial fibrillation by 11%.

**Comment:** The results of this study suggest that consumption of a Mediterranean diet supplemented with extra-virgin olive oil may prevent the development of atrial fibrillation in people who are at high risk for cardiovascular disease. These findings add to the other cardioprotective effects that have previously been observed with this diet.

Martínez-González MA et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation*. 2014;130:18–26.

### Eicosapentaenoic Acid Prevents Arrhythmia After Acute Myocardial Infarction

One hundred fifteen Japanese patients (mean age, 70 years) with an acute myocardial infarction who were undergoing percutaneous coronary intervention (PCI) were randomly assigned to receive 1800 mg per day of eicosapentaenoic acid (EPA) or no EPA, starting within 24 hours after the PCI. The primary end point was a composite of cardiac death, stroke, reinfarction, ventricular arrhythmia, or paroxysmal atrial fibrillation within 1 month. The proportion of patients who reached the primary end point was significantly lower in the EPA group than in the control group (10.5% vs. 29.3%;  $p = 0.01$ ). The beneficial effect of EPA was due largely to a decrease in the incidence of ventricular arrhythmias (7.0% vs. 20.6%;  $p = 0.03$ ).

**Comment:** This study found that EPA (one of the major fatty acids in fish oil) decreased the incidence of ventricular arrhythmias, when administered in the acute stage of myocardial infarction, after PCI. Some, though not all, previous studies have found that fish oil has antiarrhythmic effects. The mechanism by which fish oil and EPA prevent arrhythmias is not clear.

Doi M et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: A randomized, controlled study. *Int J Cardiol*. 2014;76:577–582.

### Food Allergy Triggers Coronary Artery Spasm

A 41-year-old man had recurrent episodes of inferior ST elevation on electrocardiograms and an increase in the level of troponin T (an indicator of myocardial damage). These episodes appeared to result from coronary artery spasm. Each episode occurred after the ingestion of rice. Cardiac MRI following one of these episodes confirmed an acute subendocardial infarction.

**Comment:** Histamine, which is released during allergic reactions, is capable of causing spasm of coronary arteries. I have seen 3 patients over the years who experienced episodes of angina pectoris after ingestion of specific foods to which they were allergic. In the present case report, recurrent episodes of coronary artery spasm and subsequent myocardial infarction appeared to be triggered by the ingestion of rice. While food allergy-induced coronary artery spasm seems to be

uncommon, it should be included as part of the differential diagnosis of angina.

Young W et al. ST-elevation myocardial infarction secondary to coronary artery spasm provoked by food. *BMJ Case Rep*. 2014;2014:bcr2014205222.

### Associations Between Sodium and Potassium Intake and Risk of Cardiovascular Disease

The association between 24-hour urinary excretion of sodium and potassium and the composite end point of death and major cardiovascular events was examined in a prospective cohort study of 101,945 individuals (aged 35–70 years) in 17 countries. During a mean follow-up period of 3.7 years, compared with sodium excretion of 4.00–5.99 g per day (reference range), higher sodium excretion (7 g per day or more) was associated with a significant 15% increase in the risk of the composite end point. The association between high sodium excretion and the composite end point was strongest among participants with hypertension. Compared with the reference range, sodium excretion below 3 g per day was associated with a 27% increase in the risk of the composite end point. Compared with potassium excretion of less than 1.5 g per day, higher potassium excretion was associated with a reduced risk of the composite endpoint.

**Comment:** Urinary excretion of sodium and potassium are fairly reliable indicators of dietary intake of these electrolytes. Observational studies cannot prove causation; however, the results suggest that both high and low sodium intake may increase the risk of death or cardiovascular disease. Excessive sodium intake is known to increase blood pressure in susceptible individuals (about one-third of the population), and may also lead to cardiac hypertrophy, independently of any effect on blood pressure. In addition, very low sodium intake may have a deleterious effect on the cardiovascular system, possibly by causing insulin resistance. The present study also suggests that high potassium intake is beneficial for the cardiovascular system. Potassium is known to have an antihypertensive effect, to inhibit platelet aggregation, and to stabilize cardiac electrical activity.

O'Donnell M et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612–623.

### L-Carnosine for Heart Failure

Fifty patients (mean age, 62 years) with stable heart failure (New York Heart Association class II or III) and a left ventricular ejection fraction (LVEF) of 45% or less on optimal medical therapy were randomly assigned to receive 500 mg per day of L-carnosine or no L-carnosine (control group) for 6 months. Compared with controls, patients receiving L-carnosine had a significant improvement in peak exercise workload, 6-minute walking test distance, and quality of life (as assessed by a questionnaire and a visual analogue scale). The change in LVEF did not differ between groups.

**Comment:** L-carnosine (beta-alanyl-L-histidine) is present in high concentrations in myocardial and muscle tissue. It has multiple biochemical actions, including antioxidant and anti-inflammatory activity and inhibition of protein glycosylation. This study demonstrates that the addition of 500 mg per day of L-carnosine to conventional therapy had beneficial effects on exercise performance and quality of life in patients with chronic stable heart failure.

Lombardi C et al. Effects of oral administration of orodispersible levo-carnosine on quality of life and exercise performance in patients with chronic heart failure. *Nutrition*. 2015;31:72–78.

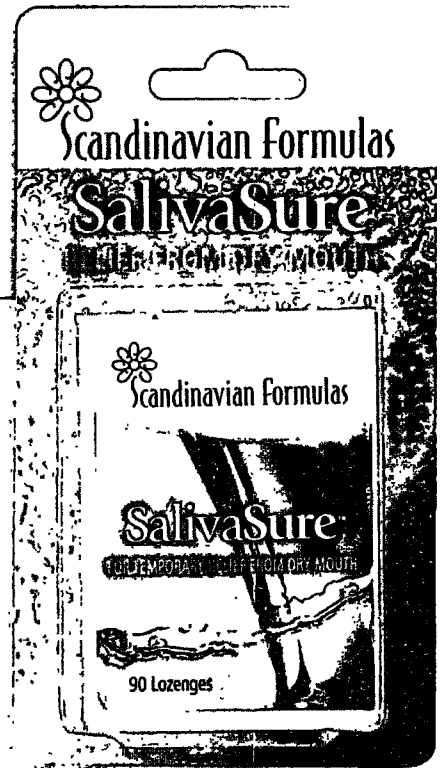


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# $\alpha$ -Cyclodextrin and Metabolic Disorders

by Stephen F. Olmstead, MD

## The Impact of Metabolic Disorders

Obesity and type 2 diabetes mellitus are pandemic metabolic disorders commonly complicated by cardiovascular disease (CVD).<sup>1,2</sup> Obesity is projected to affect over 40% of Americans in 2015.<sup>3</sup> From 1980 to 2010 the prevalence of diabetes nearly quadrupled, rising from 5.5 million persons to 21.1 million.<sup>2</sup> Worldwide, diabetes is expected to affect 592 million people by the year 2035, nearly 7% of the world's population. The conjunction of central or visceral obesity with insulin resistance, high blood pressure, elevated triglycerides, reduced high density lipoprotein (HDL) cholesterol levels, and a pro-inflammatory, prothrombotic milieu is termed *metabolic syndrome*.<sup>4</sup> People with metabolic syndrome have double the risk of developing CVD.<sup>5</sup> The risk of heart attack is increased by 3- to 4-fold, while the risk of stroke is 2- to 4-fold greater in metabolic syndrome than for people without the diagnosis.<sup>4</sup> When people with metabolic syndrome suffer a myocardial infarction or stroke, they are twice as likely to die.<sup>5</sup> Metabolic disorders represent major modifiable risk factors for CVD as well as the myriad of other associated complicating diseases.

## Standard Approaches to Metabolic Disorders

Obesity is clearly driving the increased rates of metabolic disorders.<sup>1</sup> Although obesity is increasingly appreciated as a complex systemic inflammatory metabolic disease, excessive consumption of energy-dense foods and a sedentary lifestyle are at its core. Consequently, approaches to metabolic disorders

have focused on weight loss primarily through diet and exercise.<sup>6</sup> While the merits of low-carbohydrate diets versus low-fat diets are contentiously debated, a daily reduction in calorie intake is essential to successful weight loss.<sup>1,7</sup> The daily energy deficit should be about 500 calories to sustain consistent weight reduction. Even modest weight loss delivers numerous metabolic health benefits such as reduced blood pressure, improved insulin sensitivity, decreased triglyceride levels, and increased HDL-cholesterol.<sup>8</sup> Exercise plays a crucial role in initial weight loss and healthy weight maintenance.<sup>9</sup> There is evidence exercise promotes visceral fat loss.<sup>10</sup> Even without weight loss, exercise can improve insulin sensitivity in people who had been sedentary.<sup>11</sup>

## Weight Loss: Simple in Theory, Difficult in Practice

Although the prescription of diet and exercise for metabolic disorders is simple and straightforward, in clinical practice it is challenging for people to maintain a diet and exercise regimen. Even when people are diligent, modest weight loss is the best expected outcome from participation in a structured diet program.<sup>7,12</sup> Commitment and adherence to a change in diet and lifestyle are often insurmountable barriers to involvement in a weight-loss program.<sup>13</sup> Even when initial weight loss is accomplished, long-term maintenance of the more healthful weight has proved to be a major challenge.<sup>7</sup> Clearly, additional interventions are needed to make diet and exercise more effective in metabolic disorders. One dietary intervention accepted as beneficial in

metabolic disorders is the increased intake of soluble dietary fiber, usually as oat bran, pectin, or psyllium.<sup>14</sup> The soluble fiber needs to be viscous to confer metabolic benefits.<sup>15</sup> A viscous fiber forms a gel on hydration. While recommending the increased intake of foods containing high amounts of fiber is standard advice, a supplemental soluble fiber such as psyllium in daily doses of 10 to 25 grams is generally needed to achieve improvements in insulin sensitivity, lipid levels, and body mass index. These doses are often not palatable or well tolerated. A viscous soluble dietary fiber called  $\alpha$ -cyclodextrin, offering significant potential benefits to people with metabolic disorders, is now available as a dietary supplement.

## $\alpha$ -Cyclodextrin

Cyclodextrins are naturally occurring oligosaccharides consisting of D-glucose molecules linked end-to-end by  $\alpha$ -1,4 glycosidic bonds to form a circular structure.<sup>16</sup> The molecular structure of cyclodextrins resembles a doughnut or truncated cone. Cyclodextrins derive from the action of the bacterial enzyme cyclodextrin glucosyltransferase (EC 2.4.1.19) on food starch.<sup>17</sup> Cyclodextrins are designated by a miniscule Greek letter according to the number of D-glucose molecules linked in a ring.  $\alpha$ -cyclodextrin contains 6 D-glucose molecules,  $\beta$ -cyclodextrin contains 7, and  $\gamma$ -cyclodextrin contains 8. Of these three naturally occurring cyclodextrins, the greatest interest over the years has been in  $\beta$ -cyclodextrin, as it has been relatively easy and inexpensive to produce.<sup>16</sup> However,  $\alpha$ -cyclodextrin offers the greatest

potential in metabolic disorders by virtue of three essential properties: It is highly water soluble, its glycosidic bonds are resistant to hydrolysis by human salivary and pancreatic  $\alpha$ -amylase, and it can complex with dietary fat.<sup>16</sup>

#### **$\alpha$ -Cyclodextrin and Dietary Fat**

The truncated conelike structure of  $\alpha$ -cyclodextrin was first described in 1942.<sup>18</sup> X-ray crystallography disclosed that the primary C6 hydroxyl groups on the D-glucose molecules are located on the smaller outer ring of the truncated cone, while the secondary C2 and C3 hydroxyl groups are located on the larger outer ring. This creates a highly polar ring exterior that facilitates water solubility. On the interior of the ring are found apolar hydrogens and etherlike oxygens that result in a relatively hydrophobic space within the truncated cone. This hydrophobic space allows  $\alpha$ -cyclodextrin to complex with lipophilic molecules such as the bi- and triglycerides that constitute most dietary fat. Due to its high water solubility and resistance to  $\alpha$ -amylase, an ingested dose of  $\alpha$ -cyclodextrin can pass intact and in solution through the stomach into the small intestine, where between 2% and 3% is absorbed.<sup>19</sup> When ingested with dietary fat,  $\alpha$ -cyclodextrin forms microemulsions with bi- and triglycerides.<sup>20</sup>  $\alpha$ -cyclodextrin interferes with fat absorption by preventing the hydrolysis of bi- and triglycerides into free fatty acids and glycerol. In a rodent feeding study and in-vitro experiment,  $\alpha$ -cyclodextrin has been found to complex with dietary fat in approximately a 1:9 ratio.<sup>20</sup> Given size constraints, each  $\alpha$ -cyclodextrin molecule cannot accommodate more than 1 fatty acid tail within its interior space, so  $\alpha$ -cyclodextrin molecules must combine to form microemulsions with hydrophobic interiors composed of bi- and triglycerides with  $\alpha$ -cyclodextrin-fatty acid complexes on the exterior. The  $\alpha$ -cyclodextrin-fat complexes are resistant to digestion and pass through the small intestines intact into the colon.  $\alpha$ -cyclodextrin is clearly fermented by the colon microbiota.<sup>21</sup> Evidence from a rat

study in which animals were fed a diet containing 5% w/w  $\alpha$ -cyclodextrin as well as 7% soybean oil suggested that the  $\alpha$ -cyclodextrin-fat complex was metabolized resulting in increased cecal concentrations of organic acids, especially the short-chain fatty acids acetate and propionate.<sup>22</sup> In other studies involving differing doses of  $\alpha$ -cyclodextrin and higher amounts of dietary fat,  $\alpha$ -cyclodextrin has been shown to increase fecal fat, indicating incomplete microbial fat digestion.<sup>20,23</sup>

#### **$\alpha$ -Cyclodextrin and Body Weight**

Clinical studies demonstrate  $\alpha$ -cyclodextrin's beneficial effects on weight management. In one trial, 66 obese people with diabetes mellitus were randomized to take 2 grams of  $\alpha$ -cyclodextrin as FBCx or placebo with every fat-containing meal and followed for 3 months.<sup>24</sup> All subjects had been gaining an average of  $2.2 \pm 0.88$  lbs per month before beginning the study. People who received  $\alpha$ -cyclodextrin stabilized their weight while those on placebo continued to gain weight. When weight change was normalized for dietary energy intake, people receiving  $\alpha$ -cyclodextrin lost weight. The most weight loss occurred in people who reduced energy intake while consuming  $\alpha$ -cyclodextrin.  $\alpha$ -cyclodextrin had less impact on weight in diabetics taking insulin, although it still reduced daily energy intake by 237 calories as compared with 522 calories for noninsulin users. In a double-blind, crossover study involving 41 healthy but overweight adults,  $\alpha$ -cyclodextrin alone facilitated significant weight loss over 2 months without diet or exercise.<sup>26</sup> Although none of the participants reduced their caloric intake, people receiving  $\alpha$ -cyclodextrin lost on average a little less than 1 lb during the study compared with controls. Animal studies suggest that prevention of dietary fat absorption is the principal mechanism for preventing weight gain and promoting weight loss. In a rat model of diet-induced obesity,  $\alpha$ -cyclodextrin with a high-fat diet led to a significant 22% reduction in body fat compared with control animals fed the high-fat diet alone.<sup>20</sup> In the

same animal study,  $\alpha$ -cyclodextrin significantly reduced leptin levels. Leptin is a satiety hormone made by adipocytes that normally inhibits hunger.<sup>26</sup> Leptin levels paradoxically rise with obesity due to leptin resistance or tolerance.

#### **$\alpha$ -Cyclodextrin and Dyslipidemia**

The salutary effect of  $\alpha$ -cyclodextrin on serum lipids fundamentally depends on whether dyslipidemia is present. In the clinical trial of people with diabetes,  $\alpha$ -cyclodextrin significantly lowered cholesterol levels, providing the subjects had hypertriglyceridemia on entry into the study.<sup>24</sup> The decrease in total cholesterol was due to the reduction in low-density lipoprotein (LDL) cholesterol. No change in HDL cholesterol was observed. Fasting serum triglycerides were reduced in people not using insulin, although the change did not attain statistical significance. In the study of healthy but overweight adults,  $\alpha$ -cyclodextrin significantly lowered total cholesterol and LDL-cholesterol levels in subjects entering the study with hypercholesterolemia and hypertriglyceridemia.<sup>25</sup> It also effectively lowered circulating apolipoprotein B, a lipoprotein strongly associated with an increased risk of atherosclerotic vascular plaque and coronary heart disease. In a study of 34 healthy individuals, 2 grams of  $\alpha$ -cyclodextrin significantly lower postprandial triglycerides following a standardized meal.<sup>28</sup> The magnitude of the postprandial triglyceride reduction was strongly dependent on fasting triglyceride levels. Elevated nonfasting triglycerides are an independent risk factor for ischemic heart disease and death. Animal studies suggest that  $\alpha$ -cyclodextrin may have a greater binding affinity for saturated fats and trans fatty acids.<sup>23</sup> In the LDL receptor knockout mouse model of atherosclerosis,  $\alpha$ -cyclodextrin significantly lowered plasma total cholesterol, free cholesterol, cholesterol esters, and phospholipid levels.<sup>31</sup> The mechanism whereby  $\alpha$ -cyclodextrin lowers cholesterol levels is unclear. Cholesterol is too large

## $\alpha$ -Cyclodextrin

to be complexed by  $\alpha$ -cyclodextrin. However,  $\alpha$ -cyclodextrin has been shown to complex lecithin in bile salt micelles, thereby decreasing the bile salt micellar solubility of cholesterol, which reduces absorption.<sup>32</sup> Another potential mechanism is that  $\alpha$ -cyclodextrin's properties as a prebiotic alter cholesterol's metabolism through increased short-chain fatty acid production.<sup>22,32</sup>

**$\alpha$ -Cyclodextrin and Insulin Sensitivity**  
 $\alpha$ -cyclodextrin effects a dose-dependent improvement in glucose tolerance and insulin sensitivity. When taken by healthy people together with 50 grams of digestible starch, 5- and 10-gram doses reduce the incremental area under the curve (iAUC) for postprandial glucose.<sup>33</sup> A 2-gram dose also flattened the glucose iAUC, although there were too few subjects to reach statistical significance. Studies show that cyclodextrins competitively bind and inhibit pancreatic  $\alpha$ -amylase, indicating a mechanism whereby  $\alpha$ -cyclodextrin can reduce postprandial glucose loads.<sup>34</sup> Among healthy but overweight people,  $\alpha$ -cyclodextrin decreased insulin levels by nearly 9.5%, consistent with improved insulin sensitivity.<sup>25</sup> In people with obesity and diabetes,  $\alpha$ -cyclodextrin increases adiponectin levels, especially in those not using insulin.<sup>24</sup> Higher adiponectin levels favorably affect insulin tolerance, glucose regulation, and weight reduction.<sup>26</sup>

## Conclusion

$\alpha$ -cyclodextrin is a naturally occurring soluble fiber first described in 1891.<sup>16</sup> Only recently are its potentially beneficial effects in the setting of metabolic disorders becoming better appreciated. It resists digestion by  $\alpha$ -amylase. Its steric conformation allows it to complex with the acyl tails of fatty acids, allowing the formation of microemulsions of dietary fat.  $\alpha$ -cyclodextrin can reduce fat absorption and appears to prevent weight gain and promote weight loss. In people with dyslipidemia,  $\alpha$ -cyclodextrin reduces cholesterol and LDL-cholesterol levels, and blunts the rise in postprandial triglycerides. It favorably affects insulin sensitivity in a dose-dependent manner.  $\alpha$ -cyclodextrin offers beneficial nutritional support in the setting of metabolic disorders.

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# Rauwolfia in the Treatment of Hypertension

by Douglas Lobay, Bsc, ND

*Rauwolfia serpentina* is a very safe and effective natural treatment for hypertension. This article first reviews the botany, history, and folk use of this plant. It talks about cardiologist Rustom Jal Vakil and the introduction of rauwolfia in modern medicine. It then discusses the chemical composition, pharmacology, and mechanism of action of reserpine and rauwolfia. It looks at the medical use of this plant with emphasis on its role in treating hypertension. It then critically looks at adverse side effects, toxicology, and carcinogenicity. It dispels the association between this plant and breast cancer. It further discusses the importance and screening of patients that minimizes the occurrence of depression. It concludes with a discussion of my personal experience of prescribing rauwolfia in the treatment of hypertension and recommendations for dosage.

## Botany

*Rauwolfia serpentina* is perennial shrub from the Apocynaceae, or dogbane, family. It is native to tropical and subtropical regions of Asia, including India, Burma, Bangladesh, Sri Lanka, and Malaysia. It grows in moist, warm forests to a height between 60 and 90 centimeters. It has dark green leaves that grow up to 10 centimeters long and up to 5 centimeters wide in whorls of 3 to 5 leaves. It has numerous shiny purple or black fruit that are about 0.5 centimeters in diameter. The plant has a strong, snakelike taproot that grows up to 50 centimeters in length and 2.5 centimeters in diameter.<sup>1,2</sup>

## History and Folk Use

*Rauwolfia serpentina* has been used in Indian folk medicine for thousands of years to treat a wide variety of maladies, including snake and insect bites, febrile conditions, malaria, abdominal pain, and dysentery. It was also used as a uterine stimulant, febrifuge, and cure for insanity. The plant is named after the 16th-century German physician Leonard Rauwolf, who studied it while he was traveling in India. It is reported that Indian political leader Mahatma Gandhi drank a tea made from this plant to help him relax and sleep after a long, busy day.

## Rustom Jal Vakil

Rustom Jal Vakil is the British-trained medical physician who first popularized the use of rauwolfia for the treatment of hypertension.<sup>3-5</sup> He published a watershed paper about the antihypertensive properties of *Rauwolfia serpentina* in the *British Medical Journal* in 1949. He presented detailed results of treating high blood pressure with the root of *Rauwolfia serpentina* in 50 patients. At this time, there was no effective pharmacological treatment of hypertension available anywhere in the world. This seminal paper stimulated widespread scientific research and pharmacologic interest in rauwolfia. By the end of 1949, 60,000 (90%) of Indian physicians were using rauwolfia in the treatment of hypertension. At its peak, India used 650 tonnes of the dried root per year, and worldwide usage was 20,000 tonnes per year to over 17 countries. One manufacturer claimed to have sold 94 million tablets of the dried root in 1954 alone.<sup>6</sup>

## Chemical Composition

The most important group of phytochemicals found in this plant are indole alkaloids. Over 50 different indole and indoline alkaloids have been isolated in this plant. The alkaloids are derived from amino acid tryptophan into a variety of heterocyclic ring structures. The most pharmacologically active indole alkaloids are ajmaline, deserpidine, rescinnamine, reserpine, serpentine, and yohimbine. All parts of the plant contain alkaloids, but the root has the highest amount. The exact concentration of alkaloids in the root varies from 0.7% to 3.3% of the dried weight of the root. Another more conservative estimate suggests that the total alkaloids varies from 0.8% to 1.3% of the dried weight of the plant. Other species in the same genus, including *R. caffra*, *R. canescens*, *R. heterophylla*, and *R. vomitoria*, have been found to be adulterants to *Rauwolfia serpentina*. They do contain variable amounts of indole alkaloids and may be used as a suitable alternative.<sup>7-9</sup>

## Reserpine

Reserpine is the most widely studied indole alkaloid found in this plant. In an effort by the scientific community

## Rauwolfia

to isolate a single constituent of rauwolfia, reserpine was believed to be the most pharmacologically active ingredient. The exact concentration of reserpine varies from 0.03 to 0.14% of the dry weight of the root of *Rauwolfia serpentina*. Other alkaloids believed to have medicinal action include canescine, deserpidine, recanescine, and rescinnamine. In 1952 CIBA Labs from Switzerland published the first complete report on the chemistry and pharmacology of reserpine. Also in 1952, they introduced the first isolated drug of reserpine, called Serpasil. Reserpine has a chemical formula of C<sub>33</sub>H<sub>40</sub>N<sub>2</sub>O<sub>9</sub> and a molecular mass of 609 grams, and is odorless, insoluble in water, slightly soluble in alcohol, and freely soluble in acetic acid.<sup>9-11</sup>

### Pharmacology

Reserpine has an average absorption rate of 50% after oral ingestion. Absorption occurs usually 1 to 2 hours after oral consumption, although a slower rate between 2 to 4 hours has also been reported. Reserpine is widely distributed throughout the body to the brain, liver, spleen, kidneys, and adipose tissue. It is widely distributed to red blood cells and central and peripheral neurons. It has been found in breast milk and crosses the placenta. Its initial half-life has been observed to be 4 to 5 hours. Its elimination half-life has been determined to be between 45 to 168 hours in plasma. Hepatic metabolism accounts for about 62% of the degradation of reserpine, while kidney elimination accounts for less than 8%. Up to 60% of eliminated metabolites are reserpine itself.<sup>12,13</sup>

### Mechanism of Action

The mechanism of action of reserpine is well researched. Reserpine binds to protein receptors on the membrane of specialized secretory vesicles found in the intracellular cytosol of presynaptic neurons. The membrane receptors are called vesicular monoamine transporters, or VMAT for short. The VMATs normally bind intracellular neurotransmitters, including adrenaline, noradrenaline, dopamine, histamine, and serotonin. They facilitate the transfer of these chemicals into the vesicle. The vesicle then binds to the terminal end of the presynaptic neuron and releases these chemicals into the synapse. These chemicals pass over and bind to receptors on the postsynaptic neuron and ultimately facilitate the propagation of the nervous impulse. Reserpine binds strongly to the VMAT receptor and prevents the neurotransmitters from being incorporated into the presynaptic vesicle. It thus prevents and dampens the promulgation of the nervous signal in primarily sympathetic neurons of the brain and peripheral nervous system.<sup>14,15</sup>

### Rauwolfia and Hypertension

In a clinical trial of *Rauwolfia serpentina* in essential hypertension, Vakil treated 50 patients with initial blood pressures greater than 160/95 millimeters. After 4 weeks of taking the medicine, systolic blood pressure dropped between 2 and 54 millimeters in the group of patients. 22 out of 47 patients showed a moderate drop in systolic blood pressure from 10 to 24 millimeters. 13 out of 47 patients showed a marked drop in systolic blood pressure greater than 25 millimeters. 38 out of 47 patients showed a drop in diastolic blood pressure between 4 and 34 millimeters with an average drop of 11 millimeters. 27 patients showed a moderate drop of diastolic blood pressure between 5 and 14 millimeters, and 7 patients showed a drop greater than 15 millimeters. The hypotensive action of the drug was perceptible 2 weeks after stopping the drug in 91% of patients and in 75% of patients after 4 weeks of discontinuing the drug. No serious adverse side effects were noted.<sup>16,17</sup>

In 1952, a purified standardized isolated alkaloid extract called alseroxyton was introduced to the US. The active ingredients of the purified extract were a mixture of reserpine and rescinnamine. In this study 346 patients with hypertension were treated on an outpatient basis in public and private hospitals. Original blood pressure was greater than 150/100 millimeters on admission. During the control period patients received placebo. A consistent decrease in blood pressure readings of greater than 20 millimeters was observed in patients treated with the alseroxyton extract.<sup>18</sup>

A rauwolfia product called Serpina was given to over 100 patients for periods of 1 month to 1 year. 1 to 3 Serpina tablets per daily dose were well tolerated. Its action is slow to appear from 3 to 6 days and disappears from 7 to 21 days after stopping the drug. It did not produce any serious side effects. It appears to be more effective in young, neurotic hypertensive patients with tachycardia than in those with long-established, fixed hypertension with organic, vascular disease. 39 patients with an average blood pressure reading of 192/122 millimeters and pulse of 82 were treated with Serpina alone. The average blood pressure dropped to an average of 165/95 millimeters and a pulse of 70. In 13 out of 39 patients blood pressure was controlled to normal at less than 150/90 millimeters.<sup>19</sup>

A Cochrane Database Review was undertaken to investigate the dose-related effect of reserpine on blood pressure, heart rate, and withdrawals due to adverse effects. Medical databases included Central, Embase, and Medline. Selection criteria included only truly randomized, controlled trials comparing reserpine monotherapy with placebo or no treatment in patients with primary hypertension. Four randomized controlled trials were found to meet inclusion criteria. None of the trials reported any withdrawals due to adverse effects. The authors concluded that reserpine is effective in reducing systolic blood pressure to the same degree as other first-line antihypertensive drugs. They suggested that more randomized controlled trials are needed to assess the

## Rauwolfia

effects of reserpine on blood pressure and determine the dose-related safety profile before this drug could be widely recommended as a primary antihypertensive drug.<sup>20</sup> Reserpine is also one of the few antihypertensive drugs that have been shown to produce a reduction in mortality in randomized controlled trials.<sup>21</sup>

### Adverse Side Effects and Toxicology

The most common adverse side effect of reserpine is nasal congestion that occurred in 5% to 15% of patients taking rauwolfia products. Other side effects include lethargy, sedation, psychiatric depression, hypotension, nausea, vomiting, abdominal cramping, gastric ulceration, nightmares, bradycardia, anginalike symptoms, bronchospasm, skin rash, itching and withdrawal psychosis in one case, galactorrhea, breast enlargement, and sexual dysfunction.<sup>12,22</sup> There does not appear to be an association between reserpine and cancer. Earlier studies in the late 1960s and early 1970s suggested an association between reserpine and breast cancer. A reevaluation of three original studies showed that exclusion bias played an important role in the erroneous conclusions reached.<sup>23</sup> The incidence of depression in patients taking rauwolfia and reserpine products was studied between 1954 and 1956 in an outpatient clinic. Rauwolfia and reserpine can cause depression in susceptible patients. The authors concluded that dosage is an important factor but not the sole factor involved. They advised that before starting rauwolfia therapy, a complete medical history of mental illness and depression is recommended. They further recommended that the daily dose of reserpine is limited to less than 0.75 milligrams per day.<sup>24</sup> No increased risk of birth defects has been shown in female humans who consumed reserpine at any time during their pregnancy. No mutagenic or genotoxic effects of reserpine have been demonstrated.<sup>12</sup>

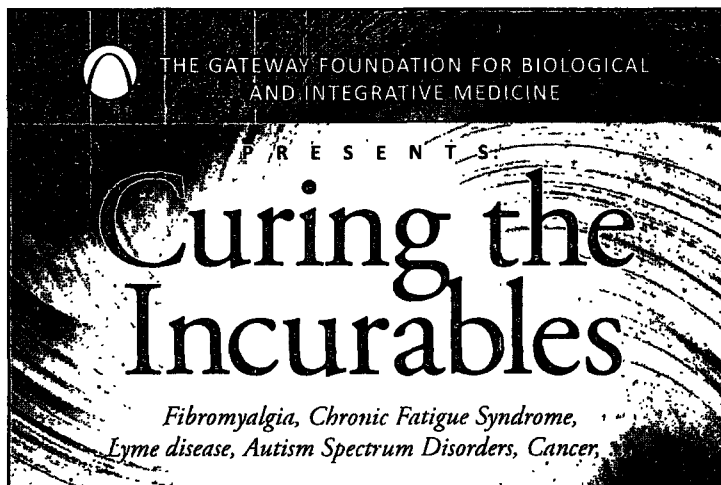
### My Experience with Rauwolfia

I have been practicing naturopathic medicine for 21 years and have tried many different herbal and mineral supplement combinations to treat hypertension. I have used rauwolfia and reserpine products alone or in combination with herbs and minerals. I currently prefer rauwolfia combined with hawthorn and some form of magnesium. I have used capsules, tablets, and tinctures, and find that I prefer encapsulated rauwolfia root powder. I have prescribed over 80,000 capsules of rauwolfia to over 300 patients with hypertension. I do not prescribe over 500 milligrams of rauwolfia per day, and usually only prescribe the equivalent of 100 milligrams of rauwolfia twice per day. Some patients I prescribe 300 to 400 milligrams per day if needed.

I support the concept of low-dose rauwolfia; the results have been amazing. I consistently see sustained blood pressure drops in most patients with hypertension. A systolic drop of 20 to 30 millimeters and a diastolic drop of 10 to 15 millimeters are normal. I have observed rauwolfia consistently work as well as other first-line

antihypertensive drugs. I have combined rauwolfia with other antihypertensive medicines. It combines well with diuretics and ACE inhibitors and ARB blockers. Caution should be exercised when the patient is on a beta blocker or calcium channel blocker. Most patients report that they feel better and less anxious and nervous. Sleep quality often improves.

I have not seen many adverse side effects. Occasional nasal congestion and loose stools have been reported. I have not seen any cases of depression. I screen all patients for history of depression and mental illness and evaluate whether they would benefit from rauwolfia therapy. I do not prescribe rauwolfia to patients who say they are depressed. Nor do I give rauwolfia to patients with congestive heart failure or cardiac decompensation, especially weak, frail elderly patients. I do not prescribe rauwolfia to patients with bradycardia or heartbeat less than 60 beats per minute. I have observed rauwolfia to lower pulse rates, usually by about 10 beats per minute in some patients. I figure that these patients may not benefit from adrenergic blockade. The potential adverse risks could potentially outweigh the benefit. I do not prescribe rauwolfia to patients who show symptoms of hypoadrenalism unless they have higher



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# Rauwolfia

▶ blood pressure, faster pulse, and symptoms of nervous anxiety.

As a rule, I do not prescribe rauwolfia to patients on prescription medicines for depression, including SSRIs, SNRIs, NDRIs, and tricyclic antidepressants. Logic dictates that there is conflict with giving rauwolfia to patients who are on drugs whose goal is to raise norepinephrine, serotonin, and other catecholamines. I also do not prescribe rauwolfia to patients on natural medicines whose goal is to raise these neurotransmitters. These natural medicines include 5-hydroxytryptophan; tyrosine; St. John's wort; and other herbal medicines that might increase norepinephrine, serotonin, or other circulating catecholamines. Although these drugs and natural medicines work on different mechanisms, it is still a contraindication to give rauwolfia with other medicines whose goal is to have the opposite effect. Exercise caution and good clinical judgment when dealing with patients who might be on these drugs and natural medicines.

I am happy and confident in my use of rauwolfia in the treatment of hypertension. In my experience, I have observed rauwolfia to be the single best natural remedy for high blood pressure.

## Conclusions

Based on a review of the literature, rauwolfia appears to be a safe and effective treatment for hypertension when used in appropriate low doses. An equivalent dose of pure rauwolfia alkaloids, also known as alseroxyton extract or pure reserpine, can also be used to treat hypertension. LDR (low-dose rauwolfia) can be safely recommended to patients who have been screened to benefit from this treatment. The total daily dose of rauwolfia should be less than 500 milligrams of root and in most cases can be less than 250 milligrams per day. The purified alkaloid alseroxyton extract would be less than 5 milligrams per day and in most cases less than 2.5 milligrams per day. The reserpine dose would be less than 500 micrograms per day and in most cases less than 250 micrograms per day. An

equivalent tincture dose would be based on the strength of the tincture. For instance, the dose of a 1:5 tincture would be 0.5 milliliters equalling 100 milligrams of crude root. In a standard dropper, 15 drops would equal 1.0 milliliters.

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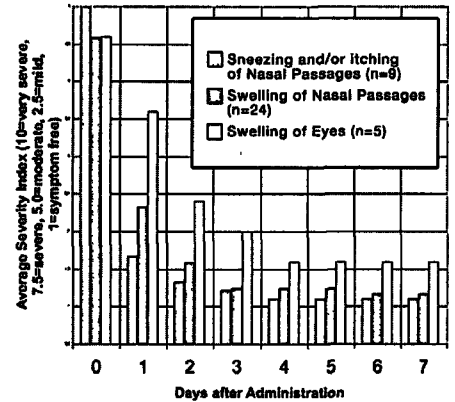
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# Omega-3s' Therapeutic Impact on Eye Care

by John W. Lahr, OD, FAAO

It has been well documented that the average American diet is out of balance when it comes to the intake of omega-6 and omega-3 fatty acids. Throughout the 20th century, the increased use of refined vegetable oils in processed foods has increased the percentage of omega-6 in our diets. It is understandable that with our fast-paced lives, people are looking for convenient foods that can be consumed quickly, which leads to increased intake of processed foods high in omega-6 and saturated fats (e.g., chips, crackers, cookies, frozen dairy products, etc.). Americans also grew up on a "meat and potatoes" diet and prefer red meat, which contains arachidonic acid (AA). AA is another form of omega-6, which can have negative effects if consumed in large quantities. It is no surprise that 80% of American diets are lacking in quality omega-3 essential fatty acids (EFAs), which are high in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

*Essential* in essential fatty acids is the key word to better understand this dietary problem. Our bodies do not produce EPA and DHA, so we must obtain these nutrients from our diet or through dietary supplements. EFAs are critical to almost every body system and function, from cell membranes to regulating inflammation. Bodies that are deficient in EFAs can lead to a host of adverse health conditions including:

- dry skin
- hypertension
- elevated triglycerides
- poor memory/unclear thinking
- inflexible joints

- delayed infant development
- inconsistent mood and behaviors
- eczema
- poor motor skills

EFAs have particular relevance for the eyes and ocular tissues. To illustrate this, consider that EPA and DHA attain their highest concentration in the ocular tissues – more than any other site in the body. Consider the important actions that each EFA has on the eye and vision systems:

- DHA
  - needed for neural and visual development
  - a structural lipid in retinal photoreceptor and synaptic membranes
  - protects against harmful light wavelengths, oxygen/free radicals, and age-associated damage to the eyes
- EPA
  - potent anti-inflammatory action
  - reduces inflammation in the vessel walls, lacrimal gland, meibomian gland, and ocular surface

Another fatty acid that should be considered is gamma-linoleic acid (GLA). While GLA is an omega-6, it has many properties of omega-3s and can provide anti-inflammatory, antiproliferative, and upregulatory actions, which allow the body's production of important antioxidants. Most individuals produce GLA from dietary linolenic acid (LA); however, individuals with high body mass index (BMI) or nutrition deficiencies such as zinc and magnesium can't produce GLA and could benefit from this fatty acid in a supplement form. Three oils provide quality GLA: borage, evening primrose, and

blackcurrant seed. Remember that GLA is an omega-6, which can lead to further imbalance of the omega-6/omega-3 ratio, so selective prescribing is recommended.

## Anterior Eye Surface

There is a group of chronic ocular diseases, categorized as ocular surface disease (OSD), that affect the outer eye and cause discomfort, light sensitivity, and blurred vision if not appropriately managed. Most people speak of these conditions as "dry eye," as this is the most common symptom. OSD is a prevalent problem for millions of Americans, with studies validating between 15% and 30% of individuals diagnosed or reporting multiple symptoms of ocular surface disease daily.<sup>1-3</sup> Females are more likely to experience OSD, and aging is a key factor as well. While there are multiple treatment options available for these diseases, concentrated triglyceride-form omega-3 supplements with EPA + DHA levels at, or above, 2000 mg per day are some of the best initial and long-term therapies available.

Treatment almost always begins with tear replacements or supplements (artificial tears). For cases of non-inflammatory dry eye, or those individuals with aqueous deficiency, a supplement drop several times a day will provide relief from most symptoms; however, there are many challenges with finding a quality tear-replacement supplement. Confusion often begins with the myriad of choices when one shops for artificial tears, with many containing antihistamines and decongestants that "get the red out," which creates vasoconstriction of the conjunctival

blood vessels. This results in a drop that feels cooling and lubricious on initial insertion, but which ultimately results in rebound dryness after a short period of time. Most artificial tears also contain preservatives, which allow for convenient use, recapping, and storage. Unfortunately preservatives can create long-term irritation if applied more frequently than 3 to 4 times daily. Finally, residence time varies among products. Residence time is the time that a drop lubricates and remains on the surface of the cornea prior to being wiped away from the ocular surface by the normal blinking action of the eyelids. Many of the artificial tears on the market have good lubricating properties, but lack long residence times.

When it comes to dry eye, the lack of secretion from glands of the eyelids is often a source of discomfort, dryness, and blurred vision. The outer layer of the tears is an oily substance secreted by the meibomian glands, which are vertically oriented in the upper and lower lids. These glands have openings located just behind the lashes to allow for the oil to flow into the tear liquid and provide a covering that prevents evaporation and provides a surface tension effect to avoid tears' regularly spilling onto a person's cheek. If these glands become inflamed, the oil thickens and the secretion is greatly reduced. Use of an oil-based tear supplement can assist with replacing the missing oil in the tear chemistry; however, these supplements do nothing to address the underlying problem, which is inflammation and the thicker meibum. This begins the cascade that can lead to a partial or complete occlusion of the meibomian gland, which is classified as a hordeolum or chalazion. These conditions can lead to moderate to extreme discomfort, and in advanced cases can create pressure on the cornea to alter the shape, which can blur vision.

There are a number of options to treat lid conditions that are classified as meibomian gland disease (MGD). Some of these are more maintenance-based such as warm compresses

and lid hygiene. MGD is a chronic condition that requires vigilance to manage. If basic lid hygiene does not prevent recurrence and comfort, the underlying cause is inflammation.

There are a number of options to reduce the inflammation associated with MGD; these include:

- topical steroids
- topical azithromycin
- oral omega-3 supplementation at levels of 3000 to 4000 mg/day
- oral doxycycline

Since topical steroids, topical azithromycin, and oral doxycycline should be used in a shorter course of therapy to reduce inflammation, omega-3 therapy at a dosage of 3000 to 4000 mg EPA + DHA daily can arrest and control inflammation and be used in long-term management of MGD.<sup>4</sup> Omega-3 therapy is often initiated along with one of the other three methods listed above to quickly manage the inflammatory cascade with a taper of the topical or oral medications after 30 to 45 days. There are numerous peer-reviewed studies and subsequent papers that show both objective and subjective improvement of MGD following omega-3 supplementation.<sup>5-8</sup>

If inflammation exists on the ocular surface, there are several options to reduce inflammation. As described above, most of the treatment options must be used in limited duration in the treatment and management of MGD, due to potential long-term adverse effects. Only cyclosporine and omega-3 therapy are appropriate for long-term treatment.

### Posterior Eye Segment

The retina reveals an even more compelling relationship to omega-3 fatty acids, with the focus on DHA. There is a rapid accumulation of DHA in the brain and retina during gestation and early postnatal life.<sup>9</sup> In fact, several studies validate that a higher concentration of DHA in infant formula resulted in improved levels of visual acuity, compared with formula that did not contain DHA.<sup>10</sup> Another study looked at preterm infant visual

acuity with and without DHA added to the formula, and found similar improved visual acuity with the DHA supplement added to the formula.<sup>11</sup>

The retina is highly vascularized with supply from the central retinal artery above and a vast network of capillaries – the choroid – beneath the organ structure that receives the visual images and transmits the signal to the occipital lobe of the brain. Several longstanding studies demonstrate that blood flow and circulation in the retina improve following supplementation with fish oil.<sup>12</sup>

Our bodies battle oxidative stress every moment of daily life, and the retina faces this challenge as well. Thankfully, DHA is converted into a lipid mediator that is responsible for protecting the delicate retinal pigment epithelial cells from oxidative damage.<sup>13</sup> DHA is most highly concentrated in the brain, photoreceptors, and retinal synapses; and, to no surprise, DHA accounts for 35% to 40% of the fatty acids within the eye structures. This concentration can only occur if the balance of omega-6 to omega-3 is controlled and at lower ratios of omega-6. Lower levels of omega-6s or LA improved the incorporation of omega-3s into the tissues with upregulation of most gene expression.

The retinal pigment epithelium (RPE) is the basement membrane of the retina and is critical to protection, support, and general health of the retinal receptors. A 2010 study describes the ability of the RPE cells to synthesize neuroprotectin D1 from DHA. Neuroprotectin D1 is shown to be a potent mediator, which evokes cell-protective, anti-inflammatory, pro-survival repair signaling, including the induction of antiapoptotic proteins and inhibition of proapoptotic proteins.<sup>13</sup> Without a stable, protective foundation, rod and cone receptor cells directly above the RPE will gradually lose the ability to receive and transmit.

A large portion of the American population is about to experience



## Omega-3s' Therapeutic Impact on Eye Care

➤ a significant increase in a condition known as macular degeneration. Wikipedia defines *macular degeneration, or age-related macular degeneration (AMD)*, as: "a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in 'dry' and 'wet' forms. It is a major cause of blindness and visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life."

The dry form of AMD is much more common, as demonstrated by the current numbers in the US:

- 13.5 million with dry AMD
- 1.5 million with wet AMD

Due to the aging of the US population, combined with a new risk – high-energy visible light (HEV) – the number of new AMD cases is projected to be 2.7 million annually through the year 2050.<sup>14</sup> At the current pace, we will have over 120 million individuals with AMD by the middle of the century, which will place a great practical and financial burden on the nation.

Macular degeneration, as the definition describes, creates decreased *central* vision, meaning the area that a person looks directly at will be blurred or dark. Imagine trying to read a newspaper but the words

are very blurry or you have a dark smudge in the center of the page. This will affect all daily vision tasks from driving to watching television, to the one task that makes a person cringe – the ability to use your smartphone as you do today!

There are some protective measures that can be employed to lessen the risk of macular degeneration or stabilize the condition should it begin:

- Limit the exposure to HEV-blue light wavelengths between 410 nm and 450 nm – these are dangerous and lead to macular changes implicated in degeneration.
- Eat a healthful diet with foods or supplements rich in carotenoids and antioxidants, and with anti-inflammatory properties.
- Quit smoking – smokers are 33% more likely to develop AMD.
- Maintain good health, which includes well-controlled blood pressure and cholesterol levels.
- Exercise regularly.

While many of these protective measures are the same as those to maintain general good health and well-being, the diet and nutritional intake, as well as protection from blue light, are of major importance. Let's first look at protection from blue light and sources of this danger. HEV is all around us in everyday life, with the sources being:

- sunlight – highest danger from 10 a.m. to 2 p.m. daily
- artificial light sources
  - incandescent bulbs (low danger)
  - fluorescent bulbs, including compact fluorescent (CFL; moderate to high danger)
  - light emitting diodes (LED; moderate to high danger)
  - high and low pressure sodium bulbs (no danger)
- cellular phone displays
- tablets
- laptop displays
- monitors, including both desktop computers and television screens

Protection from HEV involves reducing the intensity, which means simply moving the emitting device farther from the eyes or reducing the brightness of the device. A filter placed over the eyes in the form of a lens that is tinted or coated can also block the 410–450 nm wavelengths. Unfortunately, a lens that will block the targeted wavelengths is yellow-orange in color, which affects the hue and perception of images and is cosmetically unappealing to most individuals.

Another protective option is to increase the ability of the retinal tissues to provide a natural filter or barrier to lessen or eliminate the damaging effects of HEV. While almost all of the AMD studies to date have focused on individuals with moderate AMD and evaluated diet and supplements that have reduced the progression of degeneration, there are several occurring now that may allow a better understanding of prevention through diet and nutritional supplements.

The two landmark studies completed to date are the Age Related Eye Disease Study (AREDS) and a second version with modifications of the supplements (AREDS2).<sup>15,16</sup> The supplements in the AREDS2 study included vitamins C and E, zinc, lutein, zeaxanthin, and omega-3 fish oil. Both provided some understanding and direction with regard to limiting progression and loss of vision from AMD in a small percentage of subjects. There were, however, many considerations of importance in AREDS2.

- The population studied was very well nourished, with 89% taking Centrum Silver; and this would not be representative of the general population
- The omega-3 dosage was below "maintenance" by most standards with low DHA percentages, and the omega form (ethyl ester)

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# Omega-3s' Therapeutic Impact on Eye Care

has lower absorbability and bioavailability

- It is likely more difficult for nutritional interventions to halt disease progression in older individuals with early disease and a high risk of progression

Other recent studies involved individuals whose diets are either rich or deficient in omega-3s or have low ratios of omega 3 to 6, or who are taking supplements containing various amounts of EPA + DHA. The results are quite consistent and provide another opportunity to enhance the protection and health of the retinal tissues from structural changes that lead to macular degeneration.<sup>17,18</sup> One study of particular interest uses high dosage EPA + DHA (5000 mg/day) for a period of 6 months on 25 subjects with AMD with beginning visual acuity of 20/25 to 20/100. All subjects improved visual acuity from a minimum of 1 line to a maximum of 3 lines, using standardized measures.<sup>19</sup>

## Summary

When considering omega-3 oils, it is important to understand that the dosage and form will have a profound impact on the outcome of the desired treatment and management of the targeted conditions. The total amount of EPA + DHA must be 3000 to 4000 mg to reach anti-inflammatory levels, which is critical to manage the early acute phases of the anterior segment. Once inflammation is under control, maintenance levels of at least 2000 mg EPA + DHA are effective. Retina treatments begin at 2000 mg, and can range to levels of 4000 to 5000 mg.

The form of omega-3 is an equally critical consideration when assessing treatments for anterior or posterior areas of the eye. Studies comparing the ethyl ester and triglyceride forms of fish oil reveal superior bioavailability in the concentrated triglyceride form of fish oil.<sup>20</sup> With up to 70% greater absorbability, triglyceride-form fish oil concentrates

are becoming the primary choice of eye care professionals to obtain improved patient outcomes.

Overall, omega-3 fish oil high in EPA and DHA is a valuable treatment for the eye and adnexa, which provides the best option for long-term management of both anterior and posterior segment conditions.

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# Complete Diabetes Care Now that We Have TACT

by L. Terry Chappell, MD; T. Rae Neal, MSN, CNP; and  
Natalie Paphanchith, MSN, ACNP-BC

## Incidence and Cost

Diabetes is a growing epidemic in the US. According to the National Diabetes Statistics report for 2014, 21 million people in the US have been diagnosed with type 1 or type 2 diabetes. It is estimated an additional 8.1 million people are undiagnosed. The American Diabetic Association documented 86 million prediabetes diagnosis cases in 2012. Treatment and management of this disease is costly; the estimated annual cost of diabetes per year in the US is \$245 billion.

More alarming than diagnosis and cost is the impact that diabetes has on our overall health and well-being. Diabetes was listed as the 7th leading cause of death in the US in 2010. When diabetes is controlled, we reduce the risk of coexisting diseases. Unfortunately, many patients remain with an elevated

hemoglobin A1C. Uncontrolled diabetes leads to multiple micro- and macrovascular complications. Comorbidities secondary to diabetes include hypertension, hyperlipidemia, coronary artery disease, cerebral vascular accidents, chronic kidney disease, amputation, retinopathy, and neuropathy.<sup>1</sup>

## Conventional Approach to the Treatment of Diabetes

Type 2 diabetes mellitus (T2DM) is clearly linked to obesity. As the obesity rates climb, so does the diagnosis. Eighty to ninety percent of patients diagnosed with type 2 diabetes are classified as obese. The International Diabetes Foundation was quoted, "Diabetes and obesity are the biggest public health challenges of the 21st century." The link is clear; obesity drives insulin resistance and an inflammatory response. Prolonged

insulin resistance puts an extreme amount of stress on the pancreas. When resistance is accompanied by dysfunction of the pancreatic islet beta cells, that is what ultimately leads to the disease.<sup>2</sup>

A dietary goal should be to minimize refined sugars and starches. Modern carbohydrate staples, such as potatoes, breads, and cereals, have a high glycemic index (GI) and a very strong link to chronic disease.<sup>3</sup> Foods low on the GI scale such as sweet potatoes, winter squash, and beans help to stabilize blood glucose levels. This can be achieved with whole structured foods and lower GI. Clinical trials support low GI diets with greater fat content as more effective than low-fat diets at preventing complications associated with cardiovascular disease. Often a low fat diet contains the highest GI content, which leads to increased insulin resistance. Low GI diets improved whole body insulin sensitivity throughout the trials with no increase in LDL cholesterol.<sup>3</sup> Whole rice and seeds decrease circulating levels of glucose, insulin, LDL cholesterol, and fructosamine, while refined sugar and high-fructose corn syrup lead to increased risk for T2DM. Large amounts of fructose result in insulin resistance and could accelerate the development of T2DM and associated complications. Avoiding processed foods is an important step in preventing and managing diabetes.<sup>4</sup>

Many options are available to treat diabetes. As discussed above, lifestyle modifications are the initial target for

**Table 1: Antidiabetes Medications with Their Reductions in A1C and Effects on Weight**

Drug Class	Reduction in A1C (%)	Weight Effects (lb)
Insulin	> 2.5	+8.8–11.0
Inhaled insulin	1-2	+2.2–4.4
Sulfonylureas	1.6	+3.5–5.7
Repaglinide and nateglinide	0.8–1.5	+1.54–3.9
Metformin	1.5	–10.1–+0.88
Thiazolidinediones	0.8–1.0	+9.2–10.6
α-Glucosidase inhibitors	0.5–0.8	+0.0–0.44
DPP-IV inhibitors	0.5–1.0	+0.0–0.88
GLP-1 mimetic	0.6–0.8	–2.8–6.6
Amylin analogs	0.6	–3.1

Source: Hollander P. Anti-diabetes and anti-obesity medications: effects on weight in people with diabetes. *Diabetes Spectr.* July 2007;20(3):159–165. <http://spectrum.diabetesjournals.org/content/20/3/159/T1.expansion?ck=nck>.

obesity. Nutritional planning, weight loss, and diabetic education are a top priority. However, despite efforts of diet and exercise, many patients will require additional therapies. There are multiple oral medications available. Metformin is the initial medication of choice if liver and kidney functions are stable. However, if the hemoglobin A1C remains elevated after 3 months of therapy, an additional agent may be selected. Treatment of diabetes has greatly changed in the last 10 years. Use of sulfonylureas, meglitinides, and alpha-glucosidase inhibitors are less common, as innovative medications are integrating to the market.

Emerging drug classifications include thiazolidinediones, DPP-IV inhibitors, GLP agonists, and SGLT2 inhibitors. If insulin resistance remains high and oral medications and injectable noninsulin medications are not effective in maintaining glycemic control, insulin may be added. Likewise, if chronic medical conditions arise and prevent the use of certain medications, a basal-bolus regimen of insulin may be more appropriate.

### Goals of Treatment

As previously mentioned, treatment goals are targeted by the hemoglobin A1C. The A1C is a 3-month average of the patient's blood sugar. An A1C less than 5.7% is normal, prediabetic range is 5.7-6.4%, and diabetes is diagnosed if the A1C is greater than 6.5%. Once a patient is diagnosed with diabetes, The American Diabetes Association recommends an A1C goal less than 7%. However, many randomized trials that examined the effects of glycemic control did not include the frail elderly.<sup>5</sup>

Newer data points to higher health threats in the elderly population with tight glycemic control. The most common risk is severe hypoglycemia. Hypoglycemia can lead to increased falls, injury, trauma, and hospitalizations.<sup>6</sup> Also, elderly patients are more likely to experience

an adverse effect from their medications. The American Geriatric Society recommends the targeted A1C to be 8% in the elderly.<sup>7</sup> However, the A1C target is controversial among various organizations. Ultimately, goals should have an individual approach and target.

### Complementary Treatment Options and Lifestyle Measures

Complementary, alternative, integrative, or comprehensive, whatever term you choose, these additional approaches to medicine offer many options for the prevention and treatment of T2DM. The California Institute of Integral Studies and Integrative Medicine presented a paradigm shift in our health-care system at the International Congress for Clinicians in Complementary and Integrative Medicine in 2013.<sup>8</sup> Collaborative practice and interaction between disciplines will provide valuable insight toward a new health-care model. It is estimated that as much as 40% of adults use complementary and alternative medicine (CAM), with up to 34% of those patients having a chronic disease. These figures are meaningless when disclosure of CAM use is often withheld due to potential conflict with other providers.<sup>9</sup>

Personal responsibility is essential for prevention and management of diabetes. Awareness of recommended caloric intake and ideal body weight prevent the buildup of excess body fat, which can lead to cellular insulin resistance. Maintaining ideal body weight and modifying the diet to include important nutrients, limit less beneficial ingredients, and eliminate harmful options will lead to improved glycemic control.<sup>4</sup> Organic pollutants also accumulate in adipose tissue and carry destructive consequences. Sorbitol accumulation caused by environmental exposure leads to cell death and contributes to diabetic complications.<sup>4</sup> Weight loss and detoxification will improve insulin sensitivity and glucose tolerance. Losing as little as 5% of body fat

can lead to marked improvement in glycemic control and a reduction in the incidence of T2DM by up to 50%.<sup>10</sup>

Gaby also identified a gluten-free diet as delaying or preventing the development of T2DM due to the preservation of beta cells. Vegan diets improve glycemic control. Coffee is associated with a decreased risk of developing T2DM. Oolong tea is associated with a mean decrease in plasma glucose concentrations. This could be due to reducing iron absorption, which improves glycemic control. Modest increases in body iron stores have an adverse effect on glucose metabolism. Iron depletion enhances glucose utilization. Phlebotomy treatments have effectively reduced iron concentration to vegetarian levels and caused a 40% increase in insulin sensitivity.<sup>4</sup> Deferoxamine, an iron chelating agent, was used in poorly controlled DM patients with elevated ferritin levels to improve blood glucose and HbA1C levels.<sup>4</sup>

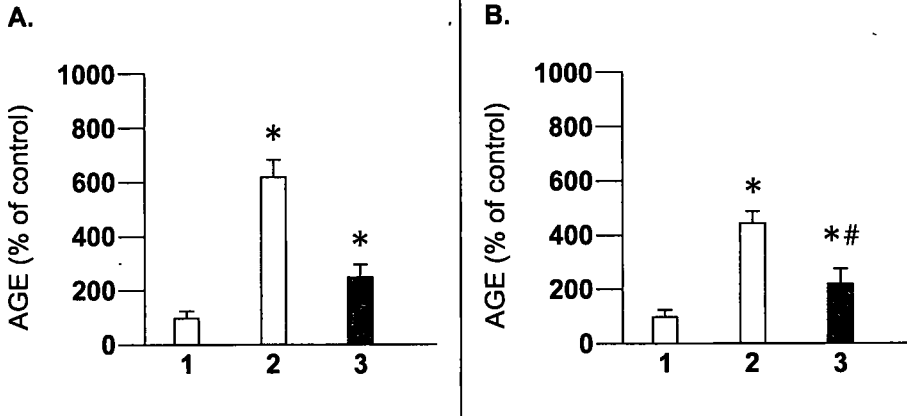
Increased dietary fiber from legumes, carrots, artichokes, peaches, strawberries, and grapefruit can improve glycemic control. Obtaining fiber from food is preferred. If supplementation is necessary, unprocessed wheat bran or apple fiber is recommended. Legumes have an ability to flatten blood sugar response over 4 hours, when eaten at breakfast.<sup>4</sup>

The temperature and manner in which food is cooked plays a role in the development of diabetes. The advanced glycation end products (AGE) remain in food after the cooking process. These products cause modifications in protein structure, which promote inflammation.<sup>4</sup> Less AGE formation results from cooking techniques using water at low temperatures for a longer period of time. An emphasis on boiling, poaching, and stewing over frying, broiling, and roasting can decrease AGE by up to 50%. AGE products play a role in the pathogenesis of insulin resistance and DM complications.<sup>4</sup>



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**Table 2**



Effect of acidic environment on the AGE content of beef. Beef (25 g) was roasted for 15 minutes at 150 °C with or without premarinating in 10 mL vinegar (A) or lemon juice (B) for 1 hour. Samples were homogenized and AGE (Nε-carboxy-methyl-lysine) content was assessed by enzyme-linked immunosorbent assay as described in the Methods section. Data are shown as % change from raw state. White bars represent raw state, gray bars roasted without marinating, and black bars marinated samples. \*Significant changes compared with the raw state ( $p < 0.05$ ). #Significant changes compared with cooked without marinating samples. 1 = raw beef; 2 = roasted beef with no vinegar or lemon; 3 = roasted beef after marinating with either vinegar or lemon for 1 hour.

Source: Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc.* 2010 Jun;110(6):911–916.e12. doi:http://dx.doi.org/10.1016%2Fj.jada.2010.03.018.

Consuming raw fats such as sesame, coconut, avocado, flaxseed, and olive oil help to reduce HbA1C. Esposito and associates found that a low-carb Mediterranean diet effectively reduced HbA1C, achieved diabetes remission, and delayed the need for medications.<sup>11</sup> Harokopio at the University of Athens found that eating plenty of olive oil, fish, and whole grains was more effective at slowing the progression of T2DM than a low-fat diet. The key factor in the Mediterranean diet is that more than 30% of daily calories are from fat. Olive oil is high in oleic acid and monounsaturated content, providing antioxidant and anti-inflammatory properties.<sup>12</sup>

Mind-body medicine, recognized by the National Center for Complementary Medicine, includes yoga, tai chi, and meditation. These techniques are used to influence the mind-body connection. Movement, breathing, meditation, and chanting

can be used to achieve lifestyle changes and stress relief, and allow inner focus. The American Diabetic Association recommends 150 minutes a week of moderate to intense physical activity. These mind-body activities can be considered moderate exercise.<sup>13</sup> No real improvement in glycemic control was seen, but beneficial effects on behavior, mood, stress, and quality of life were identified as positive outcomes.<sup>13</sup> Because chronic stress has been implicated as a risk factor for the development of T2DM and we know that stress-induced inflammatory cytokines could be the cause of this finding, it is easy to see how daily practice in mind-body medicine would have a positive effect.<sup>4</sup> Significant improvements have been documented with daily yoga training. Reduced fasting blood sugar and postprandial levels, better glycemic control, and stable autonomic control are possible with daily yoga training.<sup>9</sup>

## Supplementation

Nutritional supplementation has been effective with diabetes management. As mentioned above, various antioxidants are beneficial in preventing complications related to diabetes. The goal is to attempt to include as many fresh, nutrient-dense ingredients as possible and supplement as needed. High levels of oxidative stress have been found in diabetic patients, increasing the need for antioxidant supplementation. Deficient levels of vitamin C in diabetic patients are compounded by an impaired cellular uptake promoting hyperglycemia, which further decreases intracellular vitamin C levels. This localized deficiency contributes to end organ damage. Vitamin C supplements given at 1000 mg daily decreased urinary albumin and slowed the progression of diabetic nephropathy.<sup>4</sup>

Electrolyte disorders have been found to play an important role in the complications of diabetes and are associated with increased mortality and morbidity. Several factors affect the body's ability to utilize nutrients, including nutritional status, absorption, acid-base imbalances, pharmacokinetics, renal disease, and acute illness. This might explain why diabetic patients are found to be low in several important nutrients. Hypomagnesemia is commonly identified in diabetic patients. Magnesium is involved with more than 300 enzymatic reactions and is vital to glucose metabolism and insulin homeostasis.<sup>14</sup> Low serum and plasma levels of magnesium are associated with alterations in nerve, muscle, and cardiac conduction. This contributes to nephropathy and end stage renal disease. Nasri described a significant inverse relationship between serum magnesium and cholesterol levels.<sup>14</sup> Liamis, Liberopoulos, Barkas, and Elisaf reported that an increased dietary intake of magnesium improved metabolic control and reduced the risk of T2DM and dyslipidemia.<sup>15</sup>

The trace element chromium aids glucose with transport into the



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**Table 3: Summary of Evidence Supporting Complementary and Alternative Medicine Therapies for Type 2 Diabetes Mellitus<sup>16</sup>**

Intervention	Body Of Evidence
Cinnamon	FBG level reduction in 2 of 3 trials
Chromium	HbA1c and FBG level reduction in meta-analysis
Vanadium	FBG level reduction in uncontrolled trials
Fiber	HbA1c level reduction (nonsignificant) in 1 of 3 trials FBG level reduction in 6 of 12 trials
Green tea	FBG level reduction in 1 of 3 trials Other benefits
Bitter melon	No benefit to HbA1c or FBG levels in 2 small trials
Fenugreek	FBG level reduction in 1 of 3 trials Other benefits
Gymnema	HbA1c level reduction in 2 small trials

HbA1c: glycosylated hemoglobin A1c; FBG: fasting blood glucose.

Source: Nahas, R. *Canadian Family Physician*. 2009, (55) 591-596.

cell. Chromium deficiency induces hyperglycemia and impaired glucose tolerance. Normal chromium intake is <20 ug/day. Diet recall was used to determine the daily dietary intake of chromium. Low daily intake led to supplementing with 200 ug chromium picolinate or chromium rich yeast, which resulted in improved glucose tolerance.<sup>4</sup> The findings held true in cases of gestational diabetes mellitus.<sup>4</sup> Chromium is found in whole grains, broccoli, and grapes. Normal dietary intake ranges from 20 to 35 ug/day, based on sex and age.<sup>9</sup> Reduced HbA1C and fasting blood sugar levels were achieved with chromium supplementation. A large meta-analysis confirmed these results with a combination therapy of 600 ug chromium picolinide and 2 mg biotin.<sup>16</sup>

Biotin is a B vitamin that enhances chromium absorption and is involved with intracellular metabolism of glucose. Biotin administration of 9 to 16 mg/day improved glucose tolerance and decreased mean fasting blood sugar by 45%.<sup>4</sup> Inositol, D-chiro-inositol, and D-pinitol are found naturally in legumes and citrus fruits. D-pinitol mediates the action of insulin. When given at 20 mg/kg of body weight, a 5% decrease in plasma glucose is seen.<sup>4</sup> Vitamin D deficiency has been associated with increased glucose tolerance and diabetes. Supplementation has shown improvement in endothelial function and glucose tolerance, and an increase in insulin secretion. Doses varied from 800 to 300,000 IU/day.<sup>4</sup>

Alpha-lipoic acid (ALA) is an antioxidant. One of its many benefits includes preventing vitamin C and E deficiency, which are important to prevent and treat T2DM. Supplementing with 600 mg of ALA effectively increased insulin sensitivity, slowed the progression of complications, and prevented renal damage in T2DM patients. ALA is naturally occurring in broccoli, brussel sprouts, peas, potatoes, and yeast.<sup>17</sup>

### Herbal Preparations

Bitter melon (*Momordica charantia*) is a plant native to India and Asia. It has been used medicinally for over 600 years. Evidence has shown positive effects on glucose levels, glucose uptake, glycogen synthesis, and glucose oxidation.<sup>17</sup> Active ingredients include charantin, vicine, and polypeptide-p. Doses ranged from 150 and 2000 mg daily.<sup>18</sup> Fruit, juice, and seed extracts were also used in some studies.<sup>16</sup> Minimal side effects have been reported, although the ingredients are contraindicated in pregnancy.<sup>17</sup> Four specific compounds identified provide the biological evidence for the benefits witnessed: An example of traditional or complementary medicine providing new and effective treatments for T2DM is metformin, which originated from goat's-rue (*Galega officinalis*). Tan and associates identified bitter melon as one of the most popular botanical treatments for T2DM.<sup>19</sup>

Another promising biologic T2DM treatment is fenugreek (*Trigonella foenum-graecum*). Commonly used in Traditional Chinese Medicine for glucose control, digestive aid, and relief of menopausal symptoms, fenugreek given at 100 mg improved fasting blood glucose levels.<sup>16</sup> Fifteen grams of ground fenugreek

seed power with a meal lowered postprandial glucose levels.<sup>17</sup>

Small trials have yielded promising results for *Gymnema sylvestre*, or gumar. The leaves of this plant are used in Ayurvedic medicine to treat T2DM, high cholesterol, and obesity. Significant improvement in fasting blood sugar and HbA1C levels were obtained with doses from 200 mg to 800 mg of an extract daily.<sup>16</sup>

Cinnamon (*Cinamonum cassia*; *gui zhi* in Traditional Chinese Medicine) differs from the common spice *Cinamonum verum*. *C cassia* has been used for thousands of years to treat T2DM. The herb activates insulin receptors and increases glycogen synthesis. Five clinical trials evaluated doses from 1 to 6 grams daily and saw decreases in fasting blood glucose levels from 18 to 29 %.<sup>16</sup>

Red Korean ginseng was found to improve glucose tolerance test results, fasting plasma glucose, and blood sugar levels.<sup>20</sup> American ginseng (AG), along with an herb called konjac-mannan (KJM), may improve T2DM control and reduce complications. KJM affects the nutrient absorption rate in the small bowel, while AG affects the postabsorption activity; they work in unison to increase sensitivity and enhance secretion.<sup>21</sup>



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Doses ranged from 100 to 200 mg twice a day. Reductions in fasting plasma glucose and HbA1C were documented.<sup>17</sup>

Berberine is a compound found in goldenseal, Oregon grape, barberry, and other plants. Research has shown

it to be as effective as metformin. Doses up to 1000 mg twice daily along with lifestyle modifications led to a 7% reduction in HbA1C.<sup>22</sup> Glucose- and lipid-lowering properties were identified. Future T2DM treatment may have been identified by targeting free fatty acid metabolism.<sup>23</sup>

Publication trends in Iranian endocrinology outlined articles effective in treating T2DM. Of the 44 articles found in PubMed, Scopus, and Google Scholar, a few of the relative topics include *Silybum marianum* L. Gaertn (silymarin, or milk thistle) as an effective treatment for T2DM. Decreased serum glucose and HbA1C levels were documented in diabetic outpatients using psyllium.<sup>24</sup>

**Table 4: Selected Biologically Based Practices Used for Diabetes<sup>13</sup>**

Name	Hypothesized Effect(s) on Glucose Metabolism	Potential Adverse Effects*
<b>Botanicals</b>		
<i>Allium sativum</i> (garlic)	• Insulin secretagogue	• Blood thinning (use caution with anticoagulation or antiplatelet medications)
Aloe vera	• Insulin secretagogue	• Abdominal pain, diarrhea from laxative component, with subsequent electrolyte depletion
<i>Coccinia indica</i> (ivy gourd)	• Insulin mimetic	• None reported
<i>Gymnema sylvestre</i> (gymnema)	• Insulin secretagogue	• Suppression of sweet taste
<i>Momordica charantia</i> (bitter melon)	• Insulin mimetic • Decreased hepatic glucose production	• Glucose-6-phosphate deficiency • Contraindicated in pregnancy
<i>Opuntia streptacantha</i> (prickly pear cactus, nopal)	• Decreased carbohydrate absorption	• Diarrhea, nausea, abdominal fullness
<i>Panax ginseng</i> , <i>P. quiquefolius</i> (ginseng)	• Insulin mimetic • Alters hepatic glucose metabolism	• May interfere with effect of anticoagulation and antiplatelet medications • Estrogenic effect with breast tenderness, amenorrhea, vaginal bleeding, impotence • Hypertension • Insomnia
<i>Trigonella foenum graecum</i> (fenugreek)	• Insulin secretagogue • Decreased carbohydrate absorption	• Gas, bloating, diarrhea • Contraindicated in pregnancy
<b>Supplements</b>		
Alpha-lipoic acid	• Increased insulin sensitivity	• Monitor thyroid function in patients with thyroid disease
Chromium	• Increased insulin sensitivity	• Minimal
Coenzyme Q10	• No effect on blood glucose	• Few reported in clinical trials
Magnesium	• Insulin secretagogue • Increased insulin sensitivity	• Diarrhea, abdominal cramping • Magnesium toxicity in individuals with renal failure
Omega-3 fatty acids	• Slight increase in blood glucose	• Intake >3 g may increase risk of bleeding • Fish meat may have high levels of methylmercury; to be eaten with caution by children and pregnant/breast-feeding women • May increase LDL; caution in patients with very high LDL
Vanadium	• Insulin mimetic	• Prolonged high doses may cause renal toxicity

\*All biologically based practices that may reduce blood glucose have the potential for interacting with conventional diabetes medications, producing hypoglycemia. This is not a comprehensive list of potential adverse effects.

Source: Birdee, G.S. *Clinical Diabetes*. 2010, (28) 147-155.

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Shenyan Kangfu, based on Traditional Chinese Medicine and Zhao Enjian's work, is a traditional herbal preparation that has been improved and formulated into tablets. These consist of 11 herbal ingredients with a synergistic effect to nourish the kidney and spleen by detoxifying the body. Widely acclaimed, Shenya Kangfu has been used for DM nephropathy, based on the qi-yin deficiency syndrome: swelling, fatigue, and weak limbs. Five sites in four major cities in mainland China have been identified. Enrollment is planned for 80 patients in stage III or IV diabetic nephropathy. Enrollment began in November 2012, and 20 participants had been enrolled by March 2013.<sup>25</sup>

As outlined, there are many alternative treatments for T2DM that have been recognized as safe and effective. Small trials, meta-analyses, and anecdotal evidence provide treatment recommendations and document safety concerns, while outlining the need for additional research to improve the care that clinicians provide. The Natural Medicine Comprehensive Database states that many treatments outlined in this article are safe and effective.<sup>17</sup> The US Department of Health and Human Services contends that there is no high-quality evidence of benefit from alternative or supplemental treatments for diabetes.<sup>26</sup> We as health-care providers must combine good judgment and available evidence to offer patients the best options for maintaining optimum health.

### Chelation Therapy

Perhaps the most promising advance for the treatment of diabetes since insulin came from the Trial to Assess Chelation Therapy (TACT).<sup>27</sup> This trial emerged from a hearing of the Oversight Committee of Congress and a subsequent call for proposals by the National Institutes of Health. TACT was designed to determine if future cardiac events could be reduced for patients at least 50 years of age who had already suffered

at least one heart attack. It was a randomized, double-blind, clinical trial of 1708 patients, who were given more than 55,000 intravenous treatments. Half of the patients were given high-dose vitamins. Thus there were four groups in the study: double-placebo, high-dose vitamins without chelation, chelation with placebo vitamins, and chelation with high-dose vitamins.<sup>28</sup> All of the patients were given evidence-based, conventional care for their coronary artery disease. At the beginning of the 5 years that patients were followed, they were given 30 weekly IVs and then 10 more treatments at monthly intervals.

The benefit of EDTA chelation was shown to be statistically significant. All of the cardiac events (death, reinfarction, stroke, coronary artery revascularization, and hospitalization for severe angina) were less in the EDTA groups than in the groups that received IV placebos. All-cause mortality was also less in the treated patients. Further analysis showed that 37% of the patients had diabetes (322 EDTA and 311 placebo). For those patients with diabetes, there was a 41% reduction in cardiac events, a 52% drop in recurrent MI, and a 43% reduction in deaths. Those who received both chelation and high-dose vitamins had the best results, but even with chelation and placebo

vitamins, the NNT for major cardiac events for diabetic patients over the 5 years was 6.5. For statins in such patients, the NNT is considered to be highly effective at 17. Chelation was shown to be extremely safe when given according to protocol.<sup>27</sup>

A major action of EDTA chelation is its removal of toxic heavy metals, such as lead, cadmium, arsenic, and mercury. Such metals are proved toxic to the vascular tree from their free-radical activity.<sup>29</sup> Carlos Lamar published numerous case studies in the mid-to-late 1960s on chelation's positive effects for diabetes.<sup>30</sup> Paul Cutler found significant improvement in diabetic control with the use of the iron chelator, desferoxamine, in diabetic patients who also had high ferritin levels.<sup>31</sup> EDTA also chelates iron, but not as effectively as desferoxamine. Therapeutic phlebotomies are more effective than either desferoxamine or EDTA. The vast majority of studies on chelation therapy and vascular disease were not randomized clinical trials and were of insufficient power to draw conclusions. Few studies identified patients who had diabetes.

The authors of TACT state that the magnitude of benefit for diabetic patients calls for urgency to replicate their study.<sup>32</sup> TACT-2 has been planned to include only diabetic patients. At the same time, other

**Table 5: The Results of TACT**

Population	Endpoint	Treatment Comparison	HR	95% CI	P	5-yr NNT
Overall	Primary	EDTA v Placebo	0.82	0.69–0.99	0.035	18
Overall	Primary	EDTA + oral MVM v Placebo + placebo	0.74	0.57–0.95	0.016	12
Diabetes	Primary	EDTA v Placebo	0.59	0.44–0.79	0.0002	6.5
Diabetes	Death	EDTA v Placebo	0.57	0.36–0.88	0.011	12
Diabetes	Primary	EDTA + oral MVM v Placebo + placebo	0.49	0.33–0.75	<0.001	5.5

MVM = multivitamins and multiminerals; NNT = number needed to treat to prevent an event  
Primary endpoint = death, MI, stroke, coronary revascularization, hospitalization for angina

Source. *CardioSource World News*, December 2014:53.

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forms of vascular disease, especially peripheral vascular disease, should be studied. Hancke and Flytlie published a remarkable study demonstrating that 24 out of 27 patients on the waiting list for amputation were able to cancel their surgery and save their legs.<sup>33</sup> Chen Kuan-Hsing and associates demonstrated the effect of chelation therapy on progressive diabetic nephropathy in patients with T2DM and high lead levels.<sup>34</sup>

### Patient Decision-Making

In the meantime, TACT is clearly the best evidence available showing that chelation therapy might benefit vascular disease. The new guidelines for vascular problems call for the treating physician to have a conversation with his or her patients explaining the risks and potential benefits of all options of therapy. Then it is imperative that the patient decides what mode of therapy sounds best to him or her. This is the new "gold standard."<sup>35</sup> The patient is the decision-maker, not the doctor. Chelation therapy should be discussed in light of the evidence of TACT. If TACT-2 replicates TACT-1, chelation might be suggested for all diabetic patients. With the current status of evidence, chelation therapy should be offered to patients as an option for treatment, especially if they have signs of vascular disease.

Physicians trained in providing intravenous chelation report better overall results than TACT.<sup>36</sup> One reason that clinical practice might be better is that continued monthly maintenance is commonly offered after the basic course of treatment. TACT treated patients intravenously only for the first 20 months, but followed them for 5 years. Another reason could be that TACT did not follow patients with challenge tests for heavy metals or vascular testing to assess progressive improvement. A reaccumulation of toxic metals is not unlikely. Finally, other

nutritional therapies are often added by integrative physicians. All of these measures contribute to the best care for each individual patient and would likely improve the overall results.

Chelation therapy has been opposed by conventional doctors for many years. In 1980, the AMA effectively said to the chelation community, "Put up some evidence, or stop doing the therapy." With the help of NIH funding, and cooperation between doctors familiar with the therapy and a group of courageous cardiologists, the evidence has arrived. As clinical scientists who continually advocate evidence-based medicine, physicians are obligated to accept good evidence when it conflicts with their beliefs.<sup>37</sup> The rest of this article puts forth a comprehensive approach to diabetic patients that includes chelation therapy and alternative medicine as therapeutic options for prevention, control of the disease, avoidance of complications, and a longer lifespan.

### A Comprehensive Integrative Approach to Diabetes

First, patients must be diagnosed when they have either prediabetes or diabetes. This requires screening tests by their doctors' orders or at health fairs, especially for anyone who is overweight or has a family history of diabetes. Patients with hypoglycemia not infrequently convert to diabetes as they grow older. Fasting blood sugars are a reasonable start, but HbA1C tests are more accurate. Those who are overweight should be encouraged to eat less and better, and exercise more. Obesity is a major cause of gene expression into active diabetes.

As soon as prediabetes or diabetes is detected, a careful reassessment of lifestyle factors should be instituted. The patient and the family must embrace responsibility for controlling the disease. A healthful diet is crucial, with a special emphasis on low carbs, especially if high triglycerides

or the metabolic syndrome is present. Regular exercise and an effective way to deal with stress are important. Smoking and excessive environmental pollution are to be avoided as much as possible. Regular monitoring of lipids, HbA1C, kidney function tests such as creatinine with GFR and microalbumen, vitamin D3 levels, annual eye exams, vascular screenings, and careful attention to the feet are all required. The sensitive CRP, homocysteine, and ferritin levels should be checked at least once. A challenge test is the best way to screen for toxic metals:

Nutritional supplements can help control the disease and avoid complications. Vitamin C, biotin, chromium, magnesium, zinc, selenium, B-complex, inositol, and alpha-lipoic acid should all be considered. Several herbal supplements could also be selected if further control of the blood sugar is needed. Good candidates include cinnamon, bitter melon, and berberine. Fenugreek, *Gymnema sylvestre*, Korean or American ginseng, KJM, and combinations of herbs from India or China also might have therapeutic benefit. Milk thistle might help by its detoxification of harmful chemicals. Psyllium is also good for detox, and aids constipation. Generally, herbals are safer and less likely to cause hypoglycemia than medications.

Medications are next on the list. Oral medicines are discussed above, and insulin is a reasonable choice if needed, whether or not the patient is insulin dependent. Doctors must be careful to avoid overmedication that can lead to HbA1C readings that are too low, hypoglycemic episodes, and severe injuries, especially in the frail elderly. Control of the disease is imperative. Therapeutic goals for the HbA1C should be 6.5 to 7.0 for most patients and 8.0 for unstable elderly patients. Of course, lower levels of HbA1C are desirable if they are achieved without the help of medications.

The most dramatic evidence of treatment success in the last few years came with TACT. Chelation therapy reduced future cardiac events and lowered the death rate for patients with diabetes who had a previous myocardial infarction. The magnitude of benefit was perhaps greater than any intervention other than considerable weight loss or insulin therapy. The probable mechanism has to do with free-radical activity and inflammation caused by toxic metals, which are removed with chelation. Confirmatory research is coming with TACT-2, but cardiologists and endocrinologists should at least describe the remarkable evidence generated by TACT-1 and let patients choose whether they want chelation, either before or after significant vascular disease has developed. After all, most of the complications from diabetes are vascular, which can lead to devastating disabilities and/or premature death.

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# Managing Cardiovascular Diseases Ramblings of a Maniacal Frenetic: Pragmatic Reflections on Helping Patients Understand Their Illnesses and Treatments

by John Parks Trowbridge, MD, FACAM  
Diplomate, American Board of Clinical Metal Toxicology

My father told me, in early 1979, that he was going to see a doctor about doing chelation therapy. I went only slightly berserk, insisting that I would have heard about it in my training or residency if it had any value for cardiovascular diseases. He "wisely" stayed away from *that* charlatan. Then my mother needed drastic surgery for a bleeding ulcer in the fall of 1982. As I needed to fill my days while seeing her in San Francisco, I visited the office of Robert Haskell, MD. We discussed nutritional medicine and dietary programs ... and then he asked, "Well, you do chelation therapy, of course?" I explained my reservation about doing any treatments that were exaggerated in their claims of helping ... especially with a wide variety of illnesses. He said simply: "Come with me." We climbed up one flight of stairs. "Here," he said, "is my nurse. And my charts. And my patients. Have a good day." And what a day it was! I could barely believe the documented results of patients who had barely been able to walk due to shortness of breath or chest pains or calf pains. And I got to hear their stunning stories, in person – and to lay my hands on their bodies. I was hooked. I spent the next five months studying everything that I could find on chelation, so that I would "ace" the written exam. At the training, I met Warren Levin, MD, of New York City, clearly the best lecturer at the meeting. I spent two glorious learning days in his office; the same for Milan Packovich, MD, of Pittsburgh; also for Charles Farr, PhD, MD, of Oklahoma City; and for another eight doctors who generously offered to share their best ideas with me, so that I could strive from the start "to be the best." H. Ray Evers, MD, of Dothan, Alabama, graciously hosted me for three days to see the best of the past. And thus began my saga, to "learn more and do better than anyone else." At the very least, each of my parents and I myself benefited greatly.

## Pump, Pipes, and Performance

Cardiovascular diseases (CVD); in order to be adequately evaluated and treated, need to be classified according to the likely etiology or explanation. Simply stated, CVD are associated with the *pump* (the heart), the *pipes* (arteries of whatever size and location), and *performance* (impaired function despite adequate anatomy). One last classification – *pediatric* – will be ignored for this article, since congenital heart diseases, as genetic or developmental irregularities, have their own unique considerations. When the "pipes" involve the *venous* system, such as with thrombophlebitis, this is treated as a special case of inflammation.

## Hey, Buddy, Can You Really Treat That?

If we have incomplete or missing diagnoses, should you proceed with treatment? In fact, that complaint has been leveled at chelation therapists for years, that we fail to do "enough" diagnostic workup. If you want the details of your problem delineated down to the molecular level, go to your local university cardiologist. But if you want to feel better now and get on with your life, why not consider a treatment that works for *most* heart and blood vessel problems (and those of many other systems) that plague most people? Problems that don't improve can continue to be evaluated. The only heart problems that don't reliably show desired improvement are pediatric,

## Trowbridge's Idiot's Guidelines to Diagnosing Cardiovascular (and Other) Diseases

The following questions are essential:

1. **Who** is affected? Environmental exposures, other illnesses/operations?
2. **What** is the change (deviation) from normal structure/function?
3. **When** did these changes start? When have they progressed?
4. **Where** is the site ... of the ill organ/s? Of the *patient* (home/work/travel, present and past)?
5. **Why** did the change/s occur (preceding or associated events)?
6. **How** did the change/s develop and worsen? *This is often the most critical question. ...*

The principal part of everything is the beginning. By answering these basic "reporter's questions," a good start can be made toward diagnosis and effective early treatment. *Every* patient starts here, no matter how complex or easy. Following this list reduces your likelihood of skipping an important factor and heading in the wrong direction.

because of their distorted anatomic features. The only peripheral (or central) blood vessel problems that don't show expected improvement are ..... sorry, can't recall any.

### What Do People Really Need to Know?

For the most part, medical explanations use technical terms that confuse or oversimplifications that mislead. Using the framework presented here, concepts can easily be offered that lead patients into a fair understanding of the treatments proposed and what to expect. (Much of "doctoring" is teaching, which improves compliance dramatically.)

When discussing "heart" disease, many practitioners fail to clarify the distinctions between problems with "pipes" and those with the "pump." The vast majority of heart conditions treated with surgery involve the pipes, namely "blockage disease" in the coronary (heart) arteries. In discussing "vascular diseases," other small arteries include those in "end organs" (where blood is finally delivered to the tissues, including inside the brain). Larger arteries are those coming off the heart, going "out" to the organs, up to the head, and down the arms and legs, and these are often more amenable to surgical intervention. In a distressingly large proportion of operations at any level, surgeons often imply that "your problem has been fixed; you're as good as new," simply because larger or medium-sized pipes have been popped open (ballooned, often with a bracing stent as well), bypassed (skipped over), or reamed out (endarterectomy) and sometimes "repaired" (patched). In actual fact, operations can be performed on just a few dozen inches of arteries but the underlying problems are widespread, affecting a distressing portion of the 60,000-plus miles of blood vessels sustaining your body organs.

When patients understand the need to restore better blood flow, distinctions can be made between surgical reduction or removal of blockage compared with nonsurgical ways to improve flow. Blockage is a "plumbing" concept, easily grasped. What is harder for many patients to grasp is that better "flow" dramatically relates to incremental reduction of blockage. Increasing the central channel diameter by merely 1/6th (just 16% widening of the vessel diameter) will just about *double* the flow through that vessel. (This tiny difference is difficult

to "see" on angiogram X-ray pictures but is easily felt by the patient.) How could such blockage be gently removed? "Cardio" exercise sometimes helps. But what about reducing obstructions naturally ... through biological changes induced by IV chelation therapy? Overly simplified, EDTA chelation appears to dissolve the "mortar" that holds together the gunk that accumulates in the pipes, interfering with flow through the arteries. As the "glue" is removed, the body can safely, easily, and naturally reduce the blockage the same way that ice melts in your water glass without shattering into pieces. In fairness, sometimes very little reduction of blockage itself occurs, but gradual improvements to the nutritional status of cells can markedly improve their function and reduce symptoms earlier attributed to blockage.

When heart disease involves the "pump" portion of your heart, we're looking at three distinct sets of pathologies. First, where blood flow has been completely interrupted to a small area of muscle, that tissue actually dies (heart attack, or "infarct") and forms a scar. The scar, incidentally, might later stretch and thin out (ballooning out as an aneurysm), with a greater risk for chamber rupture ... so surgery can be advisable. Second, the cells in an area can become "sick" from reduced blood flow ("ischemia") or from nutritional deficiencies (magnesium, B-complex, even calcium), toxic accumulations (lead, mercury, arsenic, other toxic heavy metals), or other adverse changes (such as from organic toxins, pesticides, and so on). Affected muscle cells function less and less well, leading to alterations of normal contraction/relaxation patterns and pumping efficiency. Third, heart valve problems (especially for the aortic and mitral valves on the high-pressure left side) and enlargement of the aortic root or thoracic (chest) aorta are distinct anatomical problems often best treated by surgery. Recent advances are unbelievable, where certain heart valve operations (and even some large artery aneurysms) are being performed without "cracking the chest." One exception is where calcification of valve leaflets might be improved by extensive IV EDTA chelation therapy, delaying the need for urgent surgical intervention ... and even improving later operative survival.

Finally, when heart disease affects the pumping efficiency of your heart, these are "performance" issues. While

this category might "blur over" into the second pathological pattern described above, it is distinct in a number of ways. Foremost is where electrical conduction pathway "defects," for whatever reason, can lead to rhythm disruptions (atrial fibrillation, others) where the pump muscle – although otherwise functionally capable – beats erratically or less efficiently. "Cardiomyopathies" (heart muscle impairments) can result not only from rhythm malfunctions but also from viral (even bacterial, fungal, and parasitic) infections, nutritional deficiencies, toxic heavy metals such as mercury, decreased oxygen saturations, and even hormonal imbalances (hypothyroidism, perhaps deficiencies of testosterone or progesterone or others).

### The Fire Within

Inflammation is a chemical reaction, whether in organic or inorganic systems. What causes fire damage to the "outside" – to any structures, from cell organelles all the way up to observable tissues – also wreaks havoc at submicroscopic levels *inside* biological systems. At the tiniest level, we're looking at the shifting around (actually, "stealing") of electrons, with resulting conformational changes of the molecules. The concept is one of "free radicals," electron-seeking molecules, first proposed by Denham Harman, MD, in 1955. Other concepts have been advanced, many of which rely upon a basic appreciation of the central role of free radicals. For example, in 1942 Johann Björkstén proposed the cross-linkage theory to explain the "hardening" of tissues as we grow older or sicker (recall the stiff and brittle rubber band found at the back of your desk drawer). Again, electron changes are involved.

The greatest problem with free radicals is that they damage normal molecules in an accelerating pattern, somewhat like a ping-pong ball (the "initiating" radical) being thrown into a room full of mousetraps, each "loaded" with another ping pong ball. The resulting "fire" is akin to a nuclear reaction, wherein it tends to amplify and continue until it is exhausted or quenched. In the body, "antioxidants" are essential to interrupt ("quench") electron free radical damage, known as "oxidation" or inflammation. Virtually all degenerative diseases – including cardiovascular – are directly related to free radicals in their initiation and propagation, unrelentingly



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➤ through cell injury, organ dysfunction, and finally body death. These rampant oxidative changes are the common denominator, and the damages to various intracellular organelles or metabolic pathways advance in their interruption to normal function to where they are finally identified as different disease "diagnoses." Remember: all involve effectively the same inflammation chemistry.

Since the disease promulgation process is similar in widely variant tissues, this biochemical understanding opens the door to treatment programs that can have a generalized effectiveness without being specifically targeted toward any particular diagnosis. Enter chelation therapy. Clearly chelation is a dominant answer to most cardiovascular diseases. Surgical and drug interventions might still be needed, especially for more advanced disease patterns. But chelation remains the mainstay of treatment.

### The Missing Cardiovascular Diagnosis

Repeated (even *annual* for many "heart patients") treadmill EKG testing has minimal preventive value ... but pays very well. My closest contact with diagnostic limitations of a resting EKG was an older gentleman who presented with uncharacteristic discomforts at 2 in the afternoon ... a regular cardiogram was normal, but I was still suspicious. Hospitalized at my insistence to a continuously monitored bed, he suffered his heart attack at midnight. "Instant" coronary care unit response meant a dramatic reduction of otherwise likely

heart muscle damage. Repeated testing of cholesterol and triglycerides has minimal preventive value ... but pays very well. Evolving metabolic syndrome changes, once suspected by clinical presentation and slightly elevating fasting or random blood sugars, are best evaluated merely by clinical monitoring and only periodic testing of blood sugars with concurrent insulin levels. Genetic hyperlipidemias are more ominous and pose substantial survival risks, far more significant than the trivial implication of "your cholesterol is high at 230 and you need statins!" Even repeated coronary (heart) or aortic and peripheral (belly and legs) angiographic X-ray dye pictures (merely "maps" for surgery) in symptomatically stable patients have minimal preventive value and attendant appreciable risks. These invasive tests serve primarily a mapping function, to document progression of blockage advanced to the point where surgery is now desirable. And again, the angiograms pay well ... and should be reserved for *deteriorating* conditions where salvage surgery is imminent.

(A critical side comment on cholesterol: the "bad rap" that it has suffered over the past 65 years is simply undeserved. The normal response of your body to various situations is to raise cholesterol as a proper defense or adaptation. If you want to be sure that eating eggs and butter and meats does not increase heart disease, trust the observations of a scientist who spent 70 years of his life studying these issues: *Cholesterol is Not the Culprit: A Guide to Preventing Heart Disease* (2014), by Fred Kummerow, PhD – this is mandatory reading! More on cholesterol, high blood pressure, and nine other frauds in medicine: *Malignant Medical Myths:*

*Why Medical Treatment Causes 200,000 Deaths in the USA Each Year and How to Protect Yourself* (2006), by chemistry professor Joel Kaufman, PhD.)

Coronary calcium scans ("heart scans," coronary artery CT calcium scoring, also called EBCT for "electron beam") are noninvasive and useful predictive monitors for coronary events. Their value is enhanced when a sequentially rising calcium count is documented, particularly in a patient who has been asymptomatic. An exciting development is the markedly improved sensitivity of coronary MRA, magnetic resonance angiogram (imaging of heart blood vessels) without (or especially with) use of peripheral intravenous contrast. Among the most accurate "predictive" clinical tests are the carotid neck artery and abdominal aorta ultrasounds (or even CT scans), along with the noninvasive vascular lab tests for leg (peripheral) artery disease. These usually allow tracking of credible blockage and flow patterns, but they don't reflect the entire range of pathologies hidden inside the vessel walls.

The ideal predictive tests would be those that disclose unsuspected "tendencies" to develop more aggressive diseases. When a particular patient has a number of such genetic or epigenetic (variable gene expression, depending on environment and other factors) proclivities, he or she warrants more attention. Here is your "likely candidate" for more extensive and earlier blockage disease to progress. Since "pipe" problems can be imaged and measured, tests should be proposed as indicated by history, clinical exam findings, and abnormal laboratory patterns. (A simple example serves well: history of visual changes, ophthalmic exam showing blood vessel or retinal changes, with elevated blood sugars – clearly carotid artery studies are appropriate, perhaps even a brain SPECT scan, maybe others.) Unfortunately, the data are unclear regarding how best to predict the development of *non-"pipe"* pathologies – those of the pump or its performance. Cardiac muscle biopsy is not something to consider!

One predictive parameter that is grossly underemphasized is that of oxygen saturations. Numbers of studies have shown that decreasing nocturnal saturations – which reflect lowering oxygen tension in the blood and, hence, in the tissues and especially inside the

### Trowbridge's Diagnostic Testing for Dummies: Cardiovascular Diseases

The following tests *can* be useful:

(Obviously physical exam with pulse and blood pressure and respiratory rate, CBC with differential and platelets, metabolic chemistry panel, and urinalysis, 12-lead and rhythm EKG, and CXR just to be sure that "basics" are covered) ....

and

ferritin, homocysteine, fructosamine, glycohemoglobin, Vitamin D3, ESR, ANA (quantitative plus pattern), RA (quantitative), fibrinogen, uric acid, LDL low-density lipoprotein, Lp(a) lipoprotein cholesterol, small dense LDL, remnant lipoprotein (RLP) cholesterol, HDL or HDL2b cholesterol, apolipoprotein B, triglycerides.

These factors look largely at genetic or epigenetic issues, to focus treatment on those factors where free radicals matter most. Anatomic function testing, as described, is directed toward specific "problem" areas.



mitochondria energy factories of the cells – are directly related to impaired pump function and performance issues. The critical continuous generation of ATP to power cellular processes is absolutely dependent on sufficient oxygen to receive and remove electrons stripped during oxidative phosphorylation in the mitochondria. Energy production is perilously degraded when the anaerobic fermentation pathway is employed. When oxygen saturations are raised toward normal, improvements in tissue functions in all organs can be expected, including retarding of “aging” degeneration and even deferred initiation/promotion of neoplastic patterns. Otto Heinrich Warburg, MD, nominated 47 times for the Nobel prize, finally received the unshared award in physiology in 1931 for discovery of the “nature and mode of action of the respiratory enzyme.” Concluding that cancer (and other deterioration diseases) should be interpreted as a mitochondrial dysfunction, Warburg proclaimed that “the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.” As noted in Wikipedia, “When frustrated by the lack of acceptance of his ideas, Warburg was known to quote an aphorism he attributed to Max Planck: “Science progresses not because scientists change their minds, but rather because scientists attached to erroneous views die, and are replaced.” Sound familiar?

Though autoimmune issues are not the main topic for this review, practitioners should remain alert to the prospect that they might be aggravating heart and blood vessel problems. The defense system, just like all others, works optimally when oxygen tensions are sufficient, nutritional status is replete, and toxic metal and chemical exposures are minimal. When conditions are not ideal, aberrated responses are more likely and any tissue can be targeted. Since endothelial blood vessel linings are present throughout the circulatory system, any immune attack on their components can alter function – and subsequent changes can be induced in end-organ tissues anywhere. Autoimmune heart problems occur classically after untreated streptococcal infections (“strep throat”), wherein any heart tissue or the surrounding sac can suffer severe damage. Recent reports have documented antiendothelial cell

antibodies as associated with accelerated artery disease in patients with rheumatoid arthritis (RA), systemic lupus (SLE), and “spondyloarthropathies” (systemic sclerosis found with inflammatory joint diseases of the vertebral column – which can include psoriatic arthritis, inflammatory bowel disease, and so on). More autoimmune interactions will be identified in the future.

Unnoticed or misdiagnosed parasitic infections might be at the root of many diseases appearing to be autoimmune. While most people think of “worms” or “flukes,” since they are most commonly diagnosed in humans, the vast majority of parasites are single-cell organisms, extremely easy to “get,” astonishingly difficult to document or diagnose, and particularly difficult to treat. And, of course, most physicians disregard or dismiss the idea that parasites contribute that much to degenerative diseases – this oversight might be fatal to thousands of patients each year. Parasitic infections are no longer classifiable as just “diseases of the third world.” “Montezuma’s Revenge,” traveler’s diarrhea sometimes acquired in Mexico, is due to a single-cell amoeba, which (like almost all tiny parasites) is readily shared through water exposure. How many other cases of diarrhea or digestive disorders are related to unsuspected organisms? Malaria is the classic case to document endothelial blood vessel damage associated with infection. Virtually all of the world’s oceans, lakes, and rivers are teeming with parasites of some sort, found mostly in the first 9 feet below the surface. Genomic testing might become the ideal way to document some of these unwelcome residents, but many of them reside deep in tissues, where they wreak havoc. Their “stealth mode” keeps them from being “seen” until damage is profound, such as abscesses in the brain and even multiple sclerosis.

Recent discoveries of biofilms – aggregates of microorganisms within a secreted slime or protective matrix and present on virtually all moist surfaces “outside and inside” human beings (such as plaque on the teeth) – suggest that all infectious agents can be shielded from access to the immune system or antibiotics and thus could persist for years, repeatedly seeding infection that could provoke or amplify inflammation, degenerative diseases, and autoimmune responses. Complex infection patterns linked to biofilms could be more than

a passing fancy, and might indeed hold critical clues on prevention and treatment of most cardiovascular diseases. Bacterial biofilms have been found within fatty deposits of damaged arteries. Perturbations of the gut microflora are clearly related to inflammation and dysfunction of the intestinal lining. Periodontal disease (progressive gingivitis, gum inflammation) has long been associated with heart attacks and strokes. Effective dental hygiene can reduce these risks, especially important in compromised patients such as diabetics. An excellent review of how oral disease correlates with systemic health is presented in *Mouth Matters; How Your Mouth Ages Your Body and What YOU Can Do About It* (2013), by Carol Vander Stoep, RDH. Keep in mind that all these departures from normal structure and function are associated with inflammation ... and that this poses special challenges to maintenance of all cell activities.

Incidentally, as mitochondria become “sick” – such as having their chemical pathways poisoned by toxic metals – they swell with increasing calcium concentration, disrupting their shelflike cristae fold structures, dramatically interrupting the electron transport chain. Chelation therapy has been shown to repair such injured organelles, restoring more normal energy generation. So here arises the charge that chelation can be criticized for *claiming* that it “fixes everythin’, jus’ like some kinda snake-oil!” But ... patients claim (and dozens of studies by Edward McDonagh, DO, and Charles J Rudolph, DO, PhD, as well as others have documented) that chelation *does* “fix mos’ everythin’!”

All toxic metals are, to some extent, accumulating in endothelial linings and throughout heart and blood vessel cells as well – mercury, lead, cadmium, arsenic, and so on. Each has a separate contribution to amplify free radical production leading to functional impairment. Rodent studies suggest a marked intensification of damage when two or more heavy metals are present, even in trivial concentrations. But toxic heavy metals are not the only culprits. Iron is an essential element that can be present in excess (iron “storage” disorders, even mild polycythemia?),



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where it also stimulates the generation of free radicals that are especially toxic in metabolically active tissues such as liver and heart, even more so in compromised patients such as diabetics. Neurodegenerative disorders such as Alzheimer's and Parkinson's have been conclusively linked to excess iron accumulation in brain tissues. Elevated cancer rates are seen in patients with iron overload. These clinical observations confirm Warburg's contention that mitochondrial decay, mediated through amplified free radical attacks, is the root of disparate and disastrous disease patterns that steal our comfort and, ultimately, our life.

Jukka T. Salonen, MD, PhD, MPH, of Finland, reported in 1992 a prospective study of 1931 men with no symptoms of heart disease. Over the next three years from entry, the lifetime total of cigarettes smoked was determined to be the primary risk factor in those 51 patients who experienced acute myocardial infarction (heart attack). The second factor was (not cholesterol or blood sugar or blood pressure or obesity!) an elevated blood ferritin level (possibly correlated with a shift toward tissue acidosis). Beyond an accurate smoking history, this realization provides an easy laboratory test to identify those at higher risk. Ferritin levels rising ever higher above 100 ng/ml are directly associated with an alarming increasing incidence of coronary events. The iron story is, however, complicated because adequate pools of iron are essential for life. Ferritin only slowly declines after dozens of EDTA chelation treatments – correction of other metabolic perturbations is essential. Even mild iron-excess patterns might be clinically more significant than earlier appreciated.

A toxic metal side issue is now coming to the forefront: the expanding use of injectable MRI diagnostic imaging contrast agents, such as gadolinium, iron (Feridex), and manganese (Teslascan). Urinary challenge tests with D-penicillamine in some patients have shown very high excretion levels of gadolinium. The clinical significance of these findings is variable, but chelation in patients who have had repeated contrast studies might prove very valuable.

Gadolinium use has been linked to onset of rare but often crippling nephrogenic systemic fibrosis, especially in patients with reduced kidney function.

### Oversaturated with Facts?

So-called sleep apnea is associated with magnified rates and more injurious cardiac events. Sadly, most physicians have only a passing exposure at best to the parameters of at-rest oxygenation. (The awake-in-the-exam-room-chair saturation level obtained in some offices is almost useless for prediction, unless the patient is in clinical distress.) "Obstructive" events are routinely blamed for desaturation events, but my experience shows that accusation is misplaced in the vast majority. Thus, patients are subjected to "scuba-torture" (CPAP pressure mask worn during the night), usually disrupting sleep patterns for many. Further, CPAP is notorious as a failing therapy within a year of two of starting, due to minimal results (of simply blowing room air) and frustrating discomfort.

Pause to consider: if you use an "obstructive" treatment (CPAP) for a "central" problem (as interpreted from "low sats"), how likely is it to succeed? Obstructive sleep apnea is routinely "diagnosed" by sleep labs – but my observations and clinical results over the past 22 years clearly show that central apnea is far more common ... and easily controlled by nasal cannula oxygen from a home concentrator during sleep. Medicare and insurance companies concede that saturations below 89 qualify for "lifetime" oxygen support. In sharp contrast, patients with "sats" from the mid-90s on down show improvements with virtually all heart and circulation problems, mentation, arthritis, digestive disorders, strength and vitality, and so on. Recall that robust oxygen availability is essential for mitochondria to meet the metabolic demand for ATP. My testing of nocturnal oxygen saturations over the past 22-plus years has proved that the vast majority of desaturation patterns can be related to *central* causes. This central "respiratory disconnect" appears associated with past head injuries of any kind and/or toxic insults (heavy metals, organic and inorganic chemicals). Presumably hypoxic/anoxic shock and severe infections (especially meningitis and encephalitis patterns) would qualify, but my experience is too limited to offer those conclusions.

These desaturation issues present a glaring example of "the Missing Diagnosis." When "modern" medicine doesn't have (or doesn't accept) a specific treatment program, then its regimented practitioners routinely miss the accurate diagnosis for one very simple reason ... they don't look for or don't actually see the problem.

Another worthwhile topic to explore would be EECF (enhanced external counterpulsation), compression therapy wherein air pressure cuffs squeeze on the legs during the relaxation phase of the heart beat (diastole). In a surprising number of cases, augmented boluses of recently oxygenated blood surging through the coronary arteries and vital organs appear to produce a significant improvement in underlying pathology. At present, the cost and complexity of such strategies are prohibitive for many – and, again, the added benefit of supplemental oxygen during EECF treatments is likely overlooked by conventional practitioners.

### ABCD ... HFCS ....

A major change in our food processing has occurred in just the past 40-some years: the introduction of HFCS, high-fructose corn syrup, as a flavoring. Actually, more as a "sweetener." But it's not really "all natural," as we think of foods (such as glucose or sucrose [table sugar]). And it doesn't taste just exactly like sugar – but it is close enough to substitute in an astonishing number of "sweet" foods and drinks ... and even in ketchup, mayonnaise, hamburger and hotdog buns, and the like. The worst part is that it acts more like a drug than the historical sweeteners such as cane or beet sugar or honey, encouraging you to "seek more" of the HFCS-supplemented foods. You probably avoid such foods ... certainly you would recognize the chemical name. But would you tag as the same ... "corn syrup solids"? "Natural sweeteners"? "Fructose" (fruit sugar) or "fructose syrup"? "Crystalline fructose"? HFCS intake (often quickly, in soda pop, candies, cookies, "treats," cereals and baked goods, and junk foods) spikes insulin release and triggers production of triglycerides and cholesterol, let alone aggravating or actually causing intestinal permeability syndrome ("leaky gut"). Elevated insulin levels contribute to all the pathologic damage of metabolic syndrome, the preliminary to adult-onset diabetes, now epidemic in America.

Recent years have shown a 600% increase in daily consumption of HFCS, often unknowingly. Of concern are not merely obesity but also the discovery of interruption of hippocampal function (memory, orientation, even behavioral regulation) and creation of neuroinflammation. HFCS-induced inflammation has also been documented throughout sensitive endothelial tissues lining the heart and blood vessels and in joints. An association with cancer has been shown as well, supporting Warburg's insistence on mitochondrial deterioration as a primary event. The staggering number of HFCS foods are dangerous not only because of their empty-calorie content (lots of calories, devoid of real food value) leading to nutritional deficiencies, and not only because they encourage increasing intake of sugary/starchy foods, but also because these very foods sponsor the development and worsening of tooth decay, obesity, cardiovascular diseases, diabetes, and the "Yeast Syndrome."

Here's a provocative observation: HFCS foods entered the food chain in about 1971, and the first book describing the Yeast Syndrome appeared in 1978, *The Missing Diagnosis*, by Orion Truss, MD. "Syndrome X," cardiometabolic (or just metabolic) syndrome, was first described in the 1987 Banning Lecture to the American Diabetes Association by Stanford endocrinology professor Gerald Reaven, MD. This clinical pattern clearly is the developmental step toward induced diabetes and preventable cardiovascular diseases. Key pathognomonic features of metabolic (or "insulin-resistance") syndrome are the curse of our suffering survival as we age: obesity (increasing girth, elevated body mass index), higher blood pressure, elevating blood sugar (with increasing insulin production), elevating triglycerides, and decreasing HDL cholesterol. Oh – and don't even get me started on the toxic cellular effects of "other" sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharine. These were approved for limited use in foods for diabetics. Now they are widely scattered through the food chain, needlessly exposing millions to chemicals with demonstrated toxicity. (You should also be careful of Sapporo Diet Water – yes, I've seen it! – and Bernard Dehydrated Water ... an empty tin!) Incidentally, the overwhelming percentage of corn, as used in production of HFCS, is a GMO – genetically modified

for more robust growth. Some have declared these genetic manipulations by chemical giant Monsanto are the inevitable end of healthful foods. Gives you that warm, fuzzy feeling again, right?

GMO crops are engineered to resist herbicides, so higher concentrations can be applied to increase the commercial yield per acre. Are you ready for more and more hidden sources of glyphosate residues (broad-spectrum weed-killer Roundup) – now the world's largest-selling herbicide and another demon-invention from Monsanto? Glyphosate has been connected to, among a growing list of other health challenges, an increased rate of miscarriage, reduction in sex hormone production, and disruptions to endocrine system development. What about autoimmune inflammatory celiac enteropathy – classically described as "gluten intolerance"? Celiac patients experience a twofold increased risk for coronary artery disease, along with arrhythmias and heart failure. Glyphosate residues on grains might be the real culprit in the recent rise in apparent clinical patterns, since they create the setting for destructive inflammation throughout body tissues ... in not just the intestinal linings but also mitochondria.

Recent reports suggest that glyphosate interruption of cytochrome P450 detoxification enzymes, disruption of aromatic amino acid synthesis by the gut microbiome, and impaired sulfate metabolism could amplify inflammatory pathways, resulting in many degenerative diseases ... including those of the heart and blood vessels. Oddly, glyphosate "cages" (chelates?) aluminum in the gut and enhances absorption of this toxic metal. The (controversial! and challenged) speculation of glyphosate-induction of diseases has been suggested by consulting chemist Anthony Samsel and MIT computer science senior research scientist Stephanie Seneff, PhD, as the "textbook example" of "exogenous semiotic entropy": the disruption of homeostasis by environmental toxins.<sup>1</sup> But you can rest assured: the Council on Science and Public Health of the American Medical Association has concluded that "it appears unlikely that HFCS contributes more to obesity or other conditions than sucrose." Keep in mind also that the common high-fat/high-sugar diet creates hyperinsulinemia (part of the metabolic syndrome), a key factor in promoting prostate cancer. Could enhanced inflammation (promoted

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by glyphosate?) along with the yeast proliferation induced by such a diet be a major feature in cancer promotion? For years, I have treated elevated prostate specific antigen (PSA) patients aggressively for the Yeast Syndrome ... with uniformly encouraging results. For a provocative review of the crucial interrelationship of fungus (yeast) and cancer, consider this internet video by the television host of *Know The Cause* and my dear friend for over 30 years, Doug Kaufmann: <http://www.knowthecause.com/index.php/cancer>.

### Getting on with the Drugs and Stuff

You might think that I'm spending too much time and space discussing the "food issues" – and you'd be wrong. Master teacher of the American College of Cardiology, Demetrio Sodi-Pallares, MD, practicing clinical and electro-cardiology for 60 years with impoverished Mexican citizens, has long treated dramatic degenerative heart diseases with little more than radical changes in the diet. His "nontoxic therapy" evolved from low-sodium/high-potassium diet plus infusions of "polarizing" (GIK = glucose-insulin-potassium) solutions to later include a strong electromagnetic field of 200 gauss and even later use of beta blockers, thyroglobulin, and exercise.

In case you haven't yet grasped the significance of diet in development of disease, refer to the classical findings of Weston A. Price, DDS, research director for the American Dental Association, who documented the deleterious effects of "foods of commerce" (*Nutrition and Physical Degeneration: A Comparison of Primitive and Modern Diets and Their Effects*; 1939), and those of Francis M. Pottenger Jr., MD, regarding uncooked foods (reviewed in *Pottenger's Cats: A Study in Nutrition*; 1995). The Price-Pottenger Nutrition Foundation offers tremendous resources at [www.ppnf.org](http://www.ppnf.org). As the science of nutritional biochemistry advanced during the mid-1900s, our understanding of health and disease dramatically expanded.

Recall that our populations were told since the 1960s to avoid salty foods, to lower the tendency to develop high blood pressure, a major risk factor for heart disease. Sure, we have made serious efforts to avoid "salting at the



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► table." But we still eat salted peanuts, salted pretzels, salted chips, salty pickles, salty deli meats, and so on. And these salted sources don't have added iodine. Why is this an issue? Over 100 years ago, public health authorities adopted the addition of iodine to table salt, a product that virtually everyone used, in order to reduce the incidence of thyroid disease (goiter). So now we have three generations of patients who have received a steady salt intake but minimal iodine. Bingo! Broda Barnes, MD, showed some 40 years ago that low thyroid levels (associated with low iodine intake) are directly associated with a rising risk of heart attack (*Hypothyroidism: The Unsuspected Illness*; 1976). Denis Wilson MD, has shown that raising thyroid hormone levels (especially free-T3) and raising basal body temperatures closer to "normal" can lower heart disease risk, and blood tests are rarely reflective of adequate support levels (*Evidence-Based Approach to Restoring Thyroid Health*; 2014). As you might predict (note: tongue-in-cheek!), these observations continue to be challenged by the American Thyroid Association.

Magnesium holds a special place for cardiovascular diseases. Lowered intracellular levels of magnesium are difficult to detect but clearly important. When serum levels are normal, intracellular magnesium may have been scavenged to maintain that measurement. Low serum levels are, therefore, beyond critical and must be addressed, since they contribute not only to high blood pressure but also both pump (CHF, congestive heart failure) and performance (contractility and rhythm disturbances) failures, as thoroughly documented by Seelig.<sup>2</sup> Complementing magnesium certainly are manganese, copper, and zinc – adequate levels of all are essential for the formation of SOD, superoxide dismutases, thought to be the fifth most prevalent enzyme set in the human body, since they serve critical antioxidant functions in mitochondria, intracellular cytoplasm, and in extracellular fluids. SOD enzymes outcompete the essential tissue production of superoxide, used to defend against invading bacteria, protecting body cells from internally generated oxidant injury. Back to mitochondria and that inflammation

idea, right? Recently developed laboratory tests can be invaluable in helping practitioners identify patterns of nutritional deficiency that can aggravate inflammation; especially helpful are micronutrient testing to evaluate their function within leukocytes (white blood cells), urinary amino acid patterns wherein abnormalities suggest the setting for disease development or progression, and chelation challenge urinary excretion to provoke underlying essential element deficiencies, sometimes supplemented by the old standard of tissue mineral analysis by hair sampling.

Another aspect of cardiovascular disease that might relate to nutritional status and the quality of food intake involves the hypercoagulability (clotting) and rheological (flow) properties of blood. People with underlying biochemical conditions – such as diabetes, alcohol abuse, tobacco use, and even hypertension, to name a few – are more at risk for triggering abnormal clot formation. Those with "vulnerable plaque" – artery blockage that is "unstable" (inflamed and irregular in composition and shape) and more likely to have pieces "break off" and slam into tinier vessels further downstream, causing sudden vascular disasters – often suffer with a dangerous accentuation of their clotting patterns. Sometimes referred to as "sticky blood," underlying changes relate to an increased tendency to activate the clotting cascade to form a "plug" (clot or thrombus) in a blood vessel that leads to a sudden severe (even complete) interruption to flow. This ischemia pattern must be corrected as quickly as possible (infusion of a kinase "clot-buster" within 4 hours) or tissue death ensues – infarction is death of the tissue, whether heart attack, brain stroke, gangrene, retinal occlusion blindness, kidney necrosis, and so on. When a blood clot forms in deeper veins in the legs, the situation is far more ominous than painful discomfort: if dislodged, the plug can zip into the lungs, and such a pulmonary embolism can literally cause sudden death. Risks for these events are reduced by all the treatment strategies discussed along with the addition of oral "fibrinolytic" clot-buster enzymes such as nattokinase (from soy), lumbrokinase (from earthworms), or serrapeptase (from bacteria within silkworms). "Thick blood" (excessive numbers of red cells) is a different but also aggravating condition that can create similar blockage. Platelets

(tiny circulating cells responsible for starting the formation of a clot) can become "irritable" when inflammatory conditions are present (including low oxygen saturations, toxic heavy metals, toxic organic chemicals, elevated blood sugars), and their undesirable activation can amplify "sticky blood" tendencies.

A couple of last points on foods. Bioflavonoids (polyphenols), cell-signaling sugars, and a wide range of other goodies are essential for well-being. Colorful vegetables are the source of bioflavonoids (and other "live" factors) on the planet. These are critical in biological functions (believe it or stop reading the basic science journals!) and virtually all of them are now being also shown to have powerful antifungal (and even anticancer) activities. Other goodies include items such as intracellular glutathione (difficult to absorb unless enhanced by liposomal packaging, synthesis rate limited by scarce availability of L-cysteine, essential for antioxidant activity and detoxification), CoQ10, and (induced production of) nitric oxide. These latter two are critical for control of cardiovascular efficiency – pump and performance issues – while the last aids in dilatation (widening ... or reduced constriction) of the pipes. While these and other factors are not readily "replenished" by direct supplementation, their synthesis and incorporation can be encouraged by specific nutritional support beyond merely the regular "multivitamin/-mineral formulas."

### Mitochondrion Basics

Likely derived from prokaryotic ancient "bacterial" invaders into eukaryotic cells, these tiny "power plants" produce the ATP-based (adenosine triphosphate) energy used by virtually every cellular process. Cell life and division – even cell death – relate to mitochondrial status. Think of a "mito" as a "Dagwood sandwich" from the comic strip *Blondie*, with outer bread slices encasing a pile of layers of meats and cheeses. The "bread" in this illustration serves as a limiting outer membrane, through which sugars and fats can enter and ATP compounds can exit. The layers of meats and cheeses are equivalent to "shelves" (called cristae) inside the mito, stacked one upon another and separated by an insulating matrix. Enzymes and substrates involved oxidative phosphorylation (processing of sugars through to the end products of

the electron-transport system) are aligned along these shelves in specific order, much like you would search for the volume of an encyclopedia from A to Z, not randomly. When all is working well, an innocent "sugar" molecule tumbles its way along, much like a Slinky toy trips its way down stairs, going quickly from one to the next chemical reaction, in order.

Lead and other toxic heavy metals (and even iron, in excess) disrupt the inner shelf arrangements (apparently by inflammatory changes) and diminish enzyme efficiencies, reducing the rate of energy production. Further, as the mito becomes sickened and less able to perform, it can accumulate calcium ions and swell, distorting the shelf arrangements even more. While specific studies have not been done, EDTA chelation therapy appears a likely prospect to reduce internalized calcium and to restore more normal mito shape and function. Whether lead and other toxic metals are actually removed from within the mito is unclear, but in vitro laboratory studies demonstrate increased energy production in heart muscle as a result of chelation. As an interesting side note, Denham Harman, PhD, MD, who proposed the free-radical theory of aging, was frustrated by observing no increase in lifespan of research animals with the addition of antioxidant supplementation. He concluded that such nutrients did not routinely make their way into the mitochondria, which are concurrently producing as well as being damaged by free radicals. He therefore proposed the mitochondrial theory of aging in 1972, where the health of these organelles is the primary determinant of maximum lifespan.

Before settling into the comfort of "modern diagnostics and medications," be sure that exposures in the patient's setting are well understood. Especially be wary that we have less and less understanding about more and more complexities. For example, when tetraethyllead was removed from vehicle gasoline in 1976 – a good idea to reduce environmental pollution, to lower blood pressure and heart attack risk, to minimize kidney damage, to improve brain function, and so on – the replacement mineral chosen was manganese. The health hazards associated with manganese combustion products have now been debated for decades. Might we later find that our replacement is almost as challenging

to human health as the original lead that aided octane performance in the gasoline?

Another provocative speculation is that the modern practice of "polypharmacy," wherein several drugs are prescribed concurrently, might induce or amplify inflammatory processes. Medications are approved for use by the Food and Drug Administration based upon limited clinical testing, where most variables are tightly controlled. The general public, though, offers nothing but variables! The dubious interactions of multiple drugs simply haven't been studied, and their role in unwittingly aggravating disease processes – or even in inducing new ones, such as through interference with mitochondrial functions – raise disturbing questions about the bases for "modern" medical practice.

Mitochondrial dysfunctions are at the root of *all* degenerative disease progression. Understanding that optimal cellular and tissue function requires a robust supply of ATP energy leads to the obvious realization that all body activities are impaired whenever this vital component is limited. Any reduced antioxidant capability allows for unbridled inflammatory chemistry to wantonly damage cell structures and enzymes. Impairment of energy-dependent production of immune molecules leaves an undefended body increasingly prone to opportunistic attack by uncommon organisms, including those generally considered as nonpathogenic commensals or symbiotes on body surfaces, especially in the intestinal and respiratory tracts. Reduced digestive functions lead to a plethora of chemical and biological insults to gut tissues (and, subsequently, to fragile endothelial cells lining heart and blood vessels), not to mention amplification of nutritional deficiencies.

With rising challenges and diminished circulatory capacity, the physiologic strain on heart performance advances like falling dominos, inevitably resulting in degrees of kidney failure, deterioration of liver functions, accelerating diminution of gastric and pancreatic and hepatic secretions with progressive digestive impairments, peripheral circulatory embarrassment, and even organic brain syndrome. Obviously past lifestyle habits – tobacco and alcohol use, poor food choices, limited sleep, compromised stress adaptation patterns, licit and illicit drugs – create a setting (Claude

Bernard's "internal milieu") in which all of these results from mitochondrial dysfunction can accelerate more rapidly than in others with more moderate health routines. Clearly the description offered can be observed over a matter of days or weeks in preterminal patients – or can be discerned by an astute practitioner some years (even decades) before the debilitations become obvious to others.

### Putting Together the Bigger Map

While these ramblings might seem to have little to do with "cardiovascular diseases," ask yourself: "Should I be treating the damage from degenerative diseases while ignoring the environmental factors that persist and aggravate the condition?" That's rather like allowing the patient to wear the shoe causing the blister perhaps merely an hour or two a day. How foolish! Note that I do not ask whether the problem is with pipes, pump, or performance. The "diagnosis," in a classical sense, is almost irrelevant. The key is to establish the link between the condition and associated lifestyle choices and exposures so that a more comprehensive ([w]holistic!) approach can be used.

In effect, I am proposing that virtually all treatment for cardiovascular diseases should be aimed at the "utility" level. This example highlights this point: Whoever lives in a house, it matters not ... the house has the "same" utilities as found with all other houses. Whether a baker, a banker, a teacher, a postman, *you* depend upon electricity coming in and light and heat going out, depend upon water coming in and drainage and sewage going out, depend upon food and supplies coming in and trash going out. Even a driveway coming in and roads going out!

Consider each "house" to be a single "cell" of the body. Thus, a neighborhood of similar houses would constitute an "organ" and a large cluster of assembled neighborhoods would comprise a "body." Our current medical paradigm aims at treating problems within specific neighborhoods. I propose that most of our treatments should be aimed at *houses*, at the utilities provided to and functioning within the individual cells. Regardless of which utilities or cells are suffering, those are the levels at which treatments should



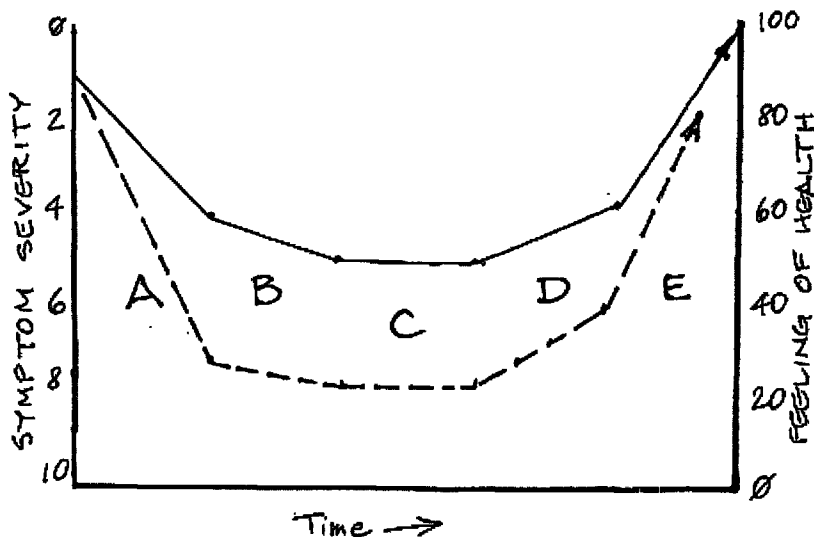
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► be aimed. This viewpoint encompasses a broader explanation of the symptoms and signs seen in illnesses, correlating the expression of disease in other organ systems (neighborhoods) that are likewise being affected by the impairment of their similar utilities.

### Changing the Slope – Oh, No! Not Calculus!

As I propose this somewhat different approach to assessment and treatment, let me offer how I describe to patients our assessment and monitoring of their conditions. Our explanation induces patients to stay with treatment programs much longer than they did before. First, let me give homage to indices such as the SF-36 Health Survey.

Consisting of 36 items, the SF-36 is a brief survey designed to assess functional health and well-being in a variety of age, disease, and control populations. ... Each question relates to one of eight domains: physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health. Results from these subscales contribute to scores for overall physical and mental health.<sup>3</sup>



The demonstrative graph is easy for patients to understand. Assume that the patient has symptom complaints, rated on our 0-to-10 scale as shown on the left side. These roughly correlate inversely to the feeling of health and wellbeing, as shown from 0 to 100 on the right side. The patient presents with declining health and worsening symptoms, as noted by the solid line above the "A." During this first phase, your job is to define the underlying issues well enough to start improving the patient's condition ... which means slowing the rate of worsening, as noted by the solid line above the "B." As you understand underlying causes better and work more with the patient, you work to hold most symptoms "level" or "unchanged," as noted by the solid line above the "C." This, in itself, is a major accomplishment ... now you have the opportunity to make a real difference for this patient.

In order to better address our particular patient population, I designed a customized "symptom-rating" form of about 50 items, printed on the flip side of our office visit notes page. At every doctor-patient visit, the patient rates his discomforts (from 0 to 10) before being seen. The various "positives" serve as foci for discussion at that meeting. Further, by "flipping up" the chart pages to earlier encounters, the progress of symptom reduction can be easily seen over time, from first visit to present time.

I describe to "newbie" patients that the first thing we're trying to do is to gain some understanding of what actually is affecting them. At this point, many patients usually will interrupt to share, once again, their various diagnoses (from other physicians), to be sure that I'm not overlooking their concerns. I acknowledge their statements and say that we understand that their various disease problems, as a whole, are worsening over time. They agree. I tell them that my first job is to identify the "pinch points," where doing something simple and deliberate will slow the rate at which they're worsening ... then level them off, so that they're no longer worsening ... then raise the slope of the curve, so that they're steadily improving ... with the ultimate goal being to return

them to more robust health, often better than that they've experienced in recent years.

This explanation encompasses a broader view of "health" more along the lines of Bircher, "a dynamic state of well-being characterized by a physical and mental potential, which satisfies the demands of life commensurate with age, culture, and personal responsibility."<sup>4</sup>

For those who need a more visual presentation, perhaps this graph might illustrate the concepts easier, since I do draw it "out in space" for patients:

During the next phase, as noted by the solid line above the "D," you are finally able to achieve some improvements and your patient clearly feels healthier. In the final phase, the solid line above the "E," results from your treatment patterns have become obvious and your patient is benefiting greatly. When you're able to establish a "maintenance program," your job is to monitor the hallmark symptoms carefully – along with relevant labs and exam findings – to "stay ahead of the curve," keeping most symptom severity scores at 3 or often less.

What about the dotted line on the graph? Some patients present to you as markedly more acute or chronically worse than anyone would like. "But doctor, I just found out about you. ..." The steeper slope above the "A" shows that you have less time to evaluate and find successful treatments. Nevertheless, your job remains the same: slow the rate of worsening, find ways to hold everything "level" while you "buy time" for treatments to work (or to be identified), then work for gradual improvement and then much more aggressive changes.

Patients who are not themselves integrative medicine physicians can have only a brief, disjointed, and even mythical view of the roots of their problems, the diagnostic finesse often needed, and the treatment options available. What they clearly understand (or at least hope for) is that doing specific actions could lead to particular, desired results. Their motivation to continue their treatment programs comes only from successful responses. Since a patient has completed our same "SF-36-type" questions at each office visit, he or she can readily see the "march" of lower and lower "scores" away from "10" and toward "0" over the course of several office encounters.

Surprisingly, many improving patients quickly forget how bad they felt or how many limitations they suffered, so

their own earlier scores are excellent reminders. In the end, when most of the answers are shifted left, "to the healthy side" (= 0 or just 1, maybe 2, occasionally 3), patients still have a visual reminder of where they started ... and how much better and happier they now feel. And that is powerful motivation to continue the maintenance programs custom designed to retain their benefits gained. Repeatedly referring to this "graph" concept during the course of therapy can dramatically aid the patient to understand and comply with the testing and treatment programs, since they can visualize "where they are" in the plan of action.

### Trowbridge's '12-Step Program' of Don'ts and Do's\*

#### Don't ...

1. assume that the "other doctors" will appreciate your participation or any patient improvements;
2. assume that the condition has been correctly diagnosed or cannot be treated;
3. assume that the present medications are not contributing to or actually causing symptomatic complaints;
4. assume that a failing course is a likely outcome for this patient at this time;
5. assume that the treatments earlier prescribed by other doctors are *correct* or even required;
6. assume that nutritional support *has little* to contribute;
7. assume that any "diet" that has been earlier counseled is *appropriate*;
8. assume that oxygen saturation levels are *sufficient*, even when not grossly abnormal;
9. assume that an *operation* is the best next choice;
10. assume that activity level seen is the *best* that can be obtained;
11. assume that your patient *understands anything at all* about his/her condition, treatment, improvement, or worsening;
12. assume that your patient is at *peace* in his/her soul.

#### Do ...

1. expect to educate your patient about the medical and political community as well as about costs and coverages for whatever you do – in person, through books and brochures, with your staff actively supporting;
2. expect that effective treatment can be started, literally, immediately and then improved upon;
3. expect that a substantial improvement is within easy reach;
4. expect that the rate of worsening can be slowed then halted for many patients ... and then "better" is "within reach";
5. expect that your assessment will reveal alternatives that have been missed, disregarded, or ignored;

6. expect that proper supplements can be, in fact, life-saving;
7. expect that radical revision of food intake can be life-saving;
8. expect that supplemental oxygen can be life-saving;
9. expect that any patient can be better prepared to survive; any needed surgery ... or to avoid it altogether;
10. expect that a gradual physical therapy program can be started immediately;
11. expect that you will need to explain the patient's condition (pipes/pump/performance, mito energy production, interrelated body functions, and so on) and basics of his/her treatment plans ... often;
12. expect that crucial spiritual encounters can be lifesaving.

\* These steps assume that appropriate medical treatment will be pursued concurrently, including detoxification of organic toxins or toxic heavy metals as needed.

### What More Is There To Learn?

Absolutely everything. The practitioner has three essential tasks. First, to learn what needs to be known about diagnosing and treating the conditions he/she holds himself out to treat. Second, to establish and oversee proper treatment programs. And third, to effectively explain to the patient and family "what it is and how we're treating it," as often as needed.

Reflecting on a lifetime career of treating "all comers," including those with cardiovascular diseases of all kinds (including two patients who were removed from the heart transplant list, due to startling improvements), I find myself struggling to offer comments of value to other practitioners. Most everyone knows the first and second tasks quite well, at least well enough to achieve basic improvements for patients. What matters, then, might be efforts to learn just a little more about how to explain the situation to the patient and

Dr. Trowbridge respectfully dedicates this article to the memory of his recently deceased friend and supportive colleague of more than 30 years, Jimmy F. Howell, MD, professor of surgery at Baylor College of Medicine for over 50 years and one of the distinguished pioneers in vascular surgery. Dr. Howell joined senior colleague H. Edward Garrett in performing the first successful coronary artery bypass operation in 1964. While director of the Vascular Surgery Training Program at Baylor and the Methodist Hospital in Houston, he oversaw the education of numerous leading national and international vascular surgeons. Dr. Howell graciously shared the podium at our 1996 public chelation celebration, "The Rumble in Humble: Heart Surgery and All that JAZZ!"

John Parks Trowbridge MD, has been certified since 1985 as a chelation diplomate by the American Board of Clinical Metal Toxicology, for which he has served as secretary. A fellow of the American College for Advancement in Medicine, he has served as director, officer, or president of several varied medical and lay associations. Popular as a professional and public speaker, he coauthored Bantam's bestselling *The Yeast Syndrome*, along with books on chelation and other topics and over 4 dozen CDs and DVDs. An interview published in the just-released book *Chelation and Other Detox Methods to Save Your Life!* presents chelation perspectives gathered over 32 years of offering this superb treatment. He provides a broad array of integrative medical therapies for challenging illness and injury problems at his solo practice, Life Celebrating Health in Humble (Houston), Texas: [jptlch@earthlink.net](mailto:jptlch@earthlink.net), 800-FIX-PAIN, [www.healthCHOICESnow.com](http://www.healthCHOICESnow.com).

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family. My methods have been successful on many levels, with patients from all backgrounds, with all conditions, and at all levels of presenting severity.

As we strive to learn better to take care of our patients, let us strive also to learn better how to *make what we do make sense* to those whose world depends on our "doing it right."

If you doubt the relevance of these concepts I've presented ... just try them! See whether patients are more receptive to your ideas of diagnosis and treatment. See whether they are more compliant – and whether they continue for maintenance programs moving them toward years of more robust health and longer, more rewarding, and vital independent and comfortable living. If you don't try them in your practice but instead ignore that they have any value, may you be blessed by this wonderful quote from Founding Father Benjamin Franklin: "Any fool can criticize, condemn and complain – and most fools do."

Enough of my foolishness.

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# Can Endurance Sports Really Cause Harm?

## The Lipopolysaccharides of Endotoxemia and Their Effect on the Heart

by Gary Huber, DO, AOBEM

The endurance athlete is viewed as a model of aerobic efficiency, possessing tremendous cardiovascular health. Certainly we can agree that exercise induces a great number of benefits to our physiology and greatly improves the quality of life, but evidence exists that excessive exercise can cause cardiovascular damage. The heavy endurance athletes such as triathletes, marathon runners, and cyclists spend hours upon hours in a state of physiologic stress. Was the human body truly built to withstand this repetitive high oxidative stress exposure? There is literature to suggest that for some, the damage caused by ischemia to the bowel and the resultant endotoxemia leads to vascular and myocardial damage that in fact increases the risk for arrhythmic and atherosclerotic change. This article is written by an endurance sport enthusiast, so it is not intended to derail such activities but rather to explore this issue of lipopolysaccharides (LPS) and the cardiac damage that occurs so that we can ascertain the true risk involved and explore options for avoidance.

In a US population of more than 300 million people, 350,000 sudden cardiac deaths, or 111 events per 100,000 people, occur annually. Within this population, we understand that risk is secondary to lifestyle, age, and a host of other factors such as the building

inflammation that often accompanies poor lifestyle and dietary decisions. But in a youthful age group who is exercising, we don't expect sudden cardiac deaths. We have all heard tragic stories of the young athlete who dies on the field only to discover that he had an undiagnosed valvular or vascular defect. But there are a significant number of cases in which no identifiable anatomical defect can be found, yet the cause of death is listed as cardiac in nature. In a well-known study by Harmon published in 2011 in the journal *Circulation*, they reported a sudden cardiac death rate of NCAA athletes of 1 per 44,000 annually, or roughly 2.3/100,000.<sup>1</sup> This might seem high, given that we are speaking of young athletes; but a look at CDC population-based data shows that cardiac-related death in the general population aged 15 to 24 is 2.5 per 100,000 people.<sup>2-5</sup>

One of the problems with the Harmon study is that the researchers did not document autopsy findings, and we are left to guess at the actual cause of cardiac death. This problem appears to be related to increased intensity of training, as the death rate is increased 2-fold from high school athletes to those on college teams.<sup>6,7</sup>

A 25-year review of autopsies in military recruits by Eckart showed a higher than expected rate of nontraumatic death at 13 per 100,000 recruits per year.<sup>8</sup> 86% of these deaths

were related to exercise. Of those determined to be cardiac in origin, 61% were secondary to coronary artery pathology. The surprising finding is that despite autopsy, 35% of deaths determined to be nontraumatic sudden death were idiopathic. Another 20% of the cardiac deaths were diagnosed as myocarditis. Is it possible that the physical demand of these recruits played a role in the idiopathic and myocarditis deaths? That is an issue worth exploring through the lens of endotoxemia.

It has been demonstrated that LPS from gram-negative bacteria adversely affects cardiomyocytes, leading to apoptotic cell death.<sup>9-12</sup> It is this apoptotic cell death that directly contributes to other forms of heart failures such as myocarditis, congestive heart disease, diabetic cardiomyopathy, chronic pressure overload, and ischemia-reperfusion injury.<sup>13-21</sup> So as we view the myocarditis, arrhythmic, and other cardiovascular deaths in athletes, we have to ask, is it possible that the very activities which we love – our endurance sports – are acting as the nidus for LPS toxicity that is poisoning our hearts?

### Defining the Problem

Engaging in prolonged endurance training or endurance events creates multiple physiologic stressors to alter our physiology. Blood flow must be



redirected from central gut and liver to the peripheral muscle mass as well as the skin to facilitate heat release. This leads to a relative bowel ischemia as the splanchnic blood flow is reduced by 80%.<sup>22-24</sup> Further exacerbating this ischemia is the simple volume loss due to sweat, the mechanical damage from the microtrauma of running, as well as thermal insult from rising body temperatures that all combine to worsen the mucosal damage occurring in the gut lining.<sup>25,26</sup> This shock-induced damage results in loss of intestinal wall integrity and death to gram-negative organisms. The cell walls of gram-negative bacteria are composed of LPS, also known as endotoxins. LPS comprise 75% of the cell walls of gram-negative bacteria, and a single gram-negative bacterial cell wall can release 1 million LPS molecules into circulation.<sup>27,28</sup>

Excessive release of LPS secondary to bowel ischemia and loss of barrier effect can overwhelm the portal circulation and the Kupffer cells' ability to neutralize them, resulting in entry to the general circulation where they cause significant adverse symptoms. The intestinal permeability induced by these sporting activities is thought to explain the high rate of occurrence of GI complaints such as diarrhea, cramps, and vomiting.<sup>29-31</sup> The occurrence of GI issues has been reported to range from 30% to 93% of all endurance athletes and represents a common problem that is often unrecognized as a serious sign of endotoxemia. Recall that LPS endotoxemia is the process of sepsis, so other sepsislike symptoms may emerge, including fever, shivering, headache, and muscle ache.<sup>32-38</sup>

Endurance training clearly taxes liver function, as demonstrated by the Moncada-Jiménez study wherein endurance athletes completing a duathlon demonstrated endotoxemia in 50% of participants.<sup>39</sup> Beyond that, all participants showed an increase in both AST and ALT level after their event. This reflects that during periods of endurance training, the reduction in splanchnic blood flow leading to bacterial death and

translocation across the intestinal wall enter the portal circulation to reach the liver and induce the acute phase response. This same finding has been demonstrated in all types of endurance sport athletes, including cyclists, marathoners, and others.<sup>40-42</sup>

Sepsis represents our best understanding of endotoxins. Patients with sepsis experience fever, dizziness, GI complaints, shivering, and cardiovascular collapse secondary to the LPS presence in the bloodstream. I would contend that if you have ever watched someone finish a marathon, the temperature regulation issues, the gut effects, the shivering, and other symptoms that occur are just a milder version of sepsis. The mechanism is the same, and unfortunately the cardiovascular risk is a part of this picture. Yes, endurance athletes are jeopardizing their heart health and potentially causing heart damage every time they train and compete. Their cardiovascular efficiency may be enhanced, but the LPS release is causing myocyte damage.

LPS can cause direct stimulation of cytokines, including TNF-alpha, which leads to severe problems; but low levels of LPS can cause damaging effects without the stimulation of cytokines. There is a multilevel response potential such that low levels of circulating LPS can cause cardiac apoptosis without stimulating excess cytokine response. It has a direct toxicity beyond its cytokine effect by directly engaging the myocyte via the toll-like receptor-4 (TLR-4).<sup>43</sup> Low levels in the nanogram-per-milliliter range can alter myocyte function.<sup>44,45</sup>

LPS can stimulate cardiac myocytes to release TNF-alpha and nitric oxide to induce apoptosis via an autocrine manner, but this level of damage occurs in the microgram/ml range. LPS at low levels does not rely on NO or TNF-alpha to cause apoptosis.<sup>46-49</sup>

So LPS exposure, whether high dose in micrograms or low dose in nanograms, has multiple mechanisms of action to induce cardiac damage. LPS in low doses (10 ng/ml) decreased the ratio of the

antiapoptotic protein Bcl-2 relative to the proapoptotic protein Bax, thus influencing apoptosis. The Li study showed that in vivo use of LPS in low dose caused a 2-fold increase in apoptosis that was blocked by the use of losartan.<sup>50</sup> The ability of LPS to independently induce apoptosis outside cytokine contribution is via stimulation of cardiac AT1 receptors. Angiotensin II induces caspase-3 enzymes which trigger apoptosis.<sup>51,52</sup> A single low dose of LPS that caused no appreciable distress and no adverse impact on blood pressure was sufficient to increase cardiac apoptosis. Low levels of LPS have been shown to be clinically relevant in multiple disease processes without causing overt distress or blood pressure changes.<sup>53-55</sup>

In the Jeukendrup study, 29 triathletes were followed with blood test before and after an Ironman distance triathlon, and a full 93% reported GI issues; 68% had endotoxemia defined as LPS levels > 5 pg/ml.<sup>56</sup> Other measures of note were IL-6 levels elevated 27-fold and CRP increased 20-fold. Interestingly, this study followed these athletes with blood measures 16 hours after the race and found that the rate of endotoxemia had increased from 68% to 79% at the 16-hour mark, demonstrating the extended effect of such physical efforts. The prealbumin level was reduced by 12%, consistent with acute phase reactions wherein the body directs efforts in making CRP and fibrinogen at the expense of making albumin and prealbumin. This is expected in the face of high CRP which was documented. In another extreme endurance event, Brocke-Utne demonstrated an endotoxemia occurrence rate of 81%.<sup>57</sup>

### **A Look at the Cellular Mechanism of Endotoxemia**

LPS in the circulation binds LBP (lipopolysaccharide binding protein) to form a complex LPS-LBP which binds to the cell membrane of Kupffer cells, reacting with the TLR-4 receptor and triggering the



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► activation and translocation of NF- $\kappa$ B.<sup>58,59</sup> So both the endotoxin and the oxidative stress of intense sporting activity induce production of NF- $\kappa$ B, thus upregulating pro-inflammatory cytokines.

LPS release causes activation of the coagulation and the complement cascade.

The pathway for this activity is through the toll-like receptor 4 (TLR-4). Cardiac myocytes express TLR-4 receptors and are susceptible to direct damage by LPS exposure.<sup>44,45,60,61</sup>

LPS stimulation of TLR-4 receptors causes depression of the myocyte contractility; they impair beta-adrenergic reactivity, and induce apoptosis through the cardiac renin-angiotensin system and the angiotensin type 1 receptors. This stimulation can lead to cardiac fibrosis.<sup>9-12, 62-66</sup>

In studies by Lew et al. in 2013, researchers exposed mice to low levels of LPS that caused no discernible clinical adverse events and yet with chronic exposure demonstrated development of fibrosis and increased mortality.<sup>66</sup> Lew et al. found that the use of losartan, which had previously been shown effective in Li's study, had no effect in their mouse model.

Mechanisms for LPS exposure include<sup>67-70</sup>:

1. sports, endurance activity, strenuous exercise
2. high-fat meals
3. periodontal disease
4. chronic type 2 diabetes
5. smoking
6. chronic infections, URIs, etc.
7. metabolic syndrome
8. cirrhosis
9. heart failure

These can cause levels of LPS in the picogram to nanogram/ml range.<sup>71</sup>

Chronic recurrent exposure of LPS by athletes can be compared to the low chronic levels of exposure seen with people with periodontal disease, smokers, chronic infections,

or chronic heart failure.<sup>72</sup> These low levels of LPS are seen in humans with chronic heart failure, suggesting a slow destructive apoptotic occurrence.

This is eerie with relation to the NCAA athletes or the military recruit studies. In Lew's study, the mice received low doses of LPS on a weekly basis, showing mild transient effects that resolved within hours. Sounds like symptoms associated with doing a hard interval workout or a long training ride. The LPS-treated mice appeared normal, with good activity and normal hemodynamic measures, including normal LV size and function, but then over time demonstrated an increased mortality with unexpected deaths. This sounds like endurance training with weekly doses of hard efforts that release LPS, causing transient symptoms and low-IgG anti-LPS levels, while causing cardiac fibrosis and apoptosis, resulting in an increased risk for sudden cardiac death which has been documented.

Short-term benefits may be seen with our innate immune response to transient inflammation. Mann's experiments, which employed a short-term preload with LPS, demonstrated a protective effect, similar to the concept of hormesis.<sup>73</sup> But he went on to report that the chronic nature of the inflammatory process of repeated LPS exposure is damaging, leading to atherosclerosis. The recurrent activation of TLR-4 is damaging to cardiovascular health and produces fibrosis of the myocyte.

LPS is involved in plaque rupture and vascular signaling. TLR-4 is upregulated and concentrated in the shoulder region of plaque, which is where rupture most commonly occurs. There is a clear association between bacterial infection and, in the case of our endurance athletes, chronic bacterial LPS exposure and the development of atherosclerosis. TLR-4-induced inflammation has been linked to plaque instability, and potential for acute coronary syndrome.<sup>73</sup>

The review by Venardos discusses the importance of myocardial antioxidant enzyme systems such as the glutathione peroxidase (GPX) and the thioredoxin reductase (TxnRed) system and their important role against oxidative stress and recovery in cardiac tissue.<sup>20</sup> The GPX and TxnRed are both selenocysteine-dependent enzymes. The sweat losses of all minerals, not the least of which are selenium, iodine, and magnesium, play a role in elevating risk; and their absence reduces myocytes' ability to withstand oxidative challenges.

### Defining Endotoxemia in Various Reports

Endotoxemia is defined as an LPS level greater than 5 pg/ml. In reviewing this literature, various definitions have been employed as well as various tests and reagents to identify it; and as such, several factors need to be taken into consideration. Depending on the reagent used and whether methods to remove LPS inhibitory substances are used, the level can vary widely. For example some reagents used to measure LPS are also sensitive to B-glucan from fungi, so use of this type of test will yield higher levels of LPS being reported. These are the factors that create confusion when comparing studies but the evidence is still greatly significant in well-controlled studies using proper reagents that LPS is real and problematic.

### Chronic effect of LPS exposure

Anti-LPS antibodies are produced by the body to bind LPS when present. These levels are lower in endurance athletes both before and after endurance events and thought to represent the chronic low levels of LPS occurring in these athletes from regular training resulting in "drainage" of adequate levels of IgG anti-LPS.<sup>74,75</sup>

There is chronic leakage of LPS secondary to long-term mucosal damage and recurrent efforts leading to low IgG anti-LPS and thus the suspicion of chronic cardiac exposure to LPS and myocyte damage. The fact

that TNF-alpha may not be detected in the blood is not a surprise, as TNF-alpha has a very short half-life, and even in patients with documented sepsis, the presence of TNF is typically only found in 4% to 54% of patients.<sup>76</sup>

We know that endurance athletes struggle with frequent upper respiratory tract infections (URI) secondary to the immune suppressive effect of their sport.<sup>77</sup> Immune suppression after extreme efforts has been documented to last for 3 to 72 hours post exertion.<sup>78</sup> The stress incurred by the HPA axis and all of the resultant immune and cytokine reactions result in a decline in the IgA levels, leaving the gut unprotected and vulnerable to barrier defects.<sup>78</sup> The simple application of vitamin C has been shown to reduce URI frequency post endurance events.<sup>79</sup>

### Treatment

As stated in the opening of this article, the goal is not to condemn endurance sports but rather understand the potential risk of damage of such activity and proceed in a manner that not only ensures greater health but likely improves athletic performance as well. There are several well-studied approaches that offer promise as well as safety in their application.

**Resveratrol** suppresses endotoxin-induced production of pro-inflammatory cytokines and activates the Nrf2 antioxidant defense pathway in vivo. Classic elevation in creatine kinase (CK) and lactate dehydrogenase (LDH) is seen with cardiac damage secondary to exposure to LPS. Hao, employing an in vivo mouse study, demonstrated that pretreatment with resveratrol significantly reduced LPS-induced elevation in CK and LDH.<sup>80</sup> Echocardiogram demonstrated a preservation of ejection fraction that had previously been reduced in the face of LPS administration. These investigators further pursued this topic by culturing human cells in LPS with resveratrol and demonstrated a significant reduction in apoptosis and

necrosis in the resveratrol cultured cells.

**Vitamin C** reduces bacterial overgrowth, and endotoxemia, and reduces the intestinal barrier defect. Vitamin C in doses of just 1000 mg prior to a significant training effort has been shown to be effective in producing a protective antioxidant effect, maintains the gut barrier effect, and reduces LPS leakage into the circulation.<sup>81</sup>

Patients with IBD, a common condition found in endurance athletes, show significantly reduced levels of vitamin C in mucosal tissue compared with non-IBD controls.<sup>82</sup> The study by Abhilash showed that vitamin C improved the integrity of mucosal tissue, reduced damage from LPS, protecting the liver and reducing fibrosis secondary to oxidative insult.<sup>83</sup>

**Lactobacillus plantarum** produces lipoteichoic acid (LTA), which has been shown to reduce LPS-induced TNF-alpha expression and downregulate the TLR-4 activity.<sup>84,85</sup> The goal with this type of treatment is to produce tolerance against the effects of LPS. Reducing the acute LPS effect may translate into reduction of the cumulative cardiovascular damage long term.

**Curcumin** has been employed for a multitude of benefits related to reduction in inflammation. Its use in the treatment of inflammatory bowel disease and inhibition of ulcer formation has been well studied and documented. Constituents of curcumin have a protective effect and inhibit intestinal spasm while increasing gastrin, secretin, bicarbonate, pancreatic enzyme, and mucous secretion.<sup>86</sup>

Turmeric's anti-inflammatory activity may lead to improvement in obesity and obesity-related diseases such as heart disease and diabetes. Curcumin interacts with hepatic stellate cells and macrophages, wherein it suppresses several cellular proteins such as transcription factor NF-kB and STAT-3, and activates Nrf2 cell signaling pathway.<sup>87</sup>

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In a 2009 study curcumin was used to block the muscle-wasting effects of LPS.<sup>88</sup> There was a dose dependent reduction in muscle loss in mice injected with LPS. Curcumin inhibited p38 kinase activity (involved in stress-induced apoptosis) in LPS-affected muscle.<sup>89</sup> Knowing the muscle-wasting effects of endurance sports in conjunction with the known release of LPS, curcumin would seem a safe and natural approach for reduction of oxidative stress and preservation of bowel function and integrity.

One last variable needs consideration in this topic. Chagnon cited evidence in 2005 of a cardiac-derived myocardial depressant factor known as macrophage migration inhibitory factor (MIF).<sup>12</sup> It appears that MIF is a critical piece to the mechanism of cardiac damage from LPS, yet its exact mechanism remains unclear. MIF is released from myocardium in response to LPS and acts as an inflammatory mediator, disrupting immune homeostasis. In a mouse study wherein investigators employed an anti-MIF antibody they were able to demonstrate a complete blockade of the LPS effect on myocytes. The blockade of MIF resulted in an increase in Bcl2/Bax ratio (an antiapoptotic result), inhibiting the release of mitochondrial cytochrome c, which in turn prevents caspase 3 activation (another antiapoptotic effect) and reduces DNA fragmentation.

Given that MIF is in fact an inflammatory mediator in immune homeostasis, it is quite possible that the multidimensional impact of resveratrol, vitamin C, and curcumin is having a direct effect on MIF. Given that these botanicals and nutrients have multiple mechanisms of action, including effects on mitochondrial function, PGC-1a, cyclooxygenase enzymes, NF-kB, and cytokine production, including TNF-alpha, their combined impact may indeed block cardiovascular damage.

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A controlled study to assess the combined impact of these protective elements on endurance athletes will likely never be done; but given the information discussed here, I think that it is more than prudent to share this approach with all endurance athletes, as it represents the potential for reducing sudden cardiac events and promoting greater health overall.

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OPTIMAL NUTRITIONAL SUPPORT

# Comprehensive Cardio Lab Work

## An Interview with Decker Weiss, NMD, FASA, and Christina Cowger

Dr. Weiss: As one of the few naturopathic cardiologists in the U.S., I've been very fortunate in my practice. Over the past 14 years, of the thousands and thousands of patients I've seen, only two have had fatal heart attacks under my care, and both were 88 years old.

That said, before I had access to comprehensive cardio testing, lab work was a real headache. If I was worried about immediate risk to a patient, I might order testing for cytokine levels. Each panel had to be ordered separately and charged individually through insurance. We know that neurotransmitters levels are also important, but if I suspected depression or some other affective disorder, I had to test for every neurotransmitter separately. With other patients, I would also do standard testing for myeloperoxidase/C-reactive protein, and in addition, have a blood draw sent to a different lab for the new oxidized-LDL marker.

Now, all this testing is available in one package in a series of panels, and that has become a complete game changer in cardio medicine. I can order any and all of these tests or a complete NeuroCardio panel from a single lab, NeuroScience. I run that entire panel on every patient at the first visit, and within one month I run the neurotransmitter and cytokine levels again to see how they are progressing with treatment. Patients also want to know if they're getting better, and they want to know that sooner rather than later.

### NeuroCardio Markers from NeuroScience

A full NeuroCardio panel provides information on immediate risk, inflammatory issues, and endothelial function, as well as neurotransmitter levels:

- cytokines – interleukin 6, 8, 10, and 17(A), and TNF- $\alpha$
- myeloperoxidase
- ApoB, ApoA1, and ApoB:ApoA1 ratio
- oxidized LDL
- high sensitivity C-reactive protein
- neurotransmitters – serotonin, norepinephrine, taurine, glycine, glutamate, and DOPAC

At one month, we do not have to re-run the tissue markers. We don't have to run the C-reactive protein or ApoB:ApoA1 ratio. They're not going to change that quickly. We do, however, need to see improvement in the cytokines and neurotransmitters within a month.

This gives me a very tangible way to motivate my patients. My rationale is something like: "This is doable – how much do you want to participate?" I can get their buy-in with the realistic promise of fast results. "I'm going to show you that within one month we can get this to improve," versus "In six months we'll re-look at the labs..."

### Motivation and Compliance

Dr. Weiss: For my patients, the ability to get measurable feedback on their progress ties in to both their motivation and their compliance. I am asking them to change their life. That means they need to look at how they go about every day and change it. In some cases, I'm asking them to change everything about their life, even their relationships. They don't want to wait three months to learn whether it's working or not. They don't want to wait six months or a year to find out if they've actually accomplished anything. That's the beauty of tracking neurotransmitters and cytokines. These levels will change (and hopefully improve) within a month so you can quickly see whether your treatment is on the right track, and if the patient is being compliant. Occasionally you may be missing the mark altogether, and you need to take a new look at that patient. In those cases, you don't want to wait three months or six months to find out that this was the wrong approach to treatment (because they just had a second heart attack). With this testing, if what you are doing isn't working, you will know within one month.

### Context

Ms. Cowger: Before you had access to the various NeuroCardio panels, how were you piecing this information together? What would the standard of care have been over

the last two decades, in terms of both laboratory testing and clinical care? Would you simply have run a cholesterol panel and seen the patient again in six months? And how is this making a difference in your practice clinically today?

Dr. Weiss: Most of the testing never strayed from a standard lipid panel. Even when C-reactive protein tests became available, most cardiologists never ran those levels because there wasn't really a drug for elevated CRP. They might opt to lower those levels with statins, but since statins were already considered first-line therapy, that particular result would not have changed clinical decision making. So they might include CRP, or they might not. The lab work never really varied from the gold standard of the lipid panel. Over time the lipid panel evolved from four or five different markers to a number of different subsets of cholesterol, but ultimately most patients ended up on statin therapy or cholesterol lowering therapy in general.

### **Sicker, Younger**

Ms. Cowger: I imagine that the expanded lab work is going to identify a whole spectrum of the population that has been at risk and gone undiagnosed.

Dr. Weiss: We're seeing people at age 35 and 40 having heart attacks. In cardiology, patients are getting younger and younger as our food supply worsens. The economic pressure keeps going up, and stimulant use keeps going up.... With the expanded lab work, we are going to be able to look at these people and say, "You might not have elevated C-reactive protein because you're only 35, but I'm concerned about your neurotransmitter levels, and your cytokines are elevated. At this point it's a race between cancer and heart disease and you're way too young to have either one."

The lab work provides us with an early warning system that identifies the patient's current state of risk. The panels take us through every parameter that we need to know as cardiologists.

### **Gender Issues**

Ms. Cowger: As a woman I have a special interest in cardiovascular disease and how it relates to women's health. When I look at the data, it seems that men far outweigh women statistically in cardiovascular disease until women enter mid-life and beyond. The rates almost equal out at that point.

Dr. Weiss: Yes, they do. Women go from a cardio risk that affects one in seven pre-menopausally, to a risk that affects *one in three* menopausally, or in post-menopause. We know that in low estrogen states the vascular walls and the endothelial lining can become damaged. We're not exactly sure at what stage that occurs. We don't know. That's why everyone thought that if we gave women estrogen, their hearts were going to be better. But rather than estrogen, we gave them dangerous synthetic copies of estrogen.

### **Estrogen and Serotonin**

Dr. Weiss: Women need estrogen post-menopausally to maintain the lining of their blood vessels. But vascular health is also intimately related to serotonin levels. There are all sorts of arguments about how estrogen and serotonin link, and the science gets quite complex. What I can tell you is that we're not really settled on exactly the interaction, but we do know that you have to check the levels of both. If a doctor is going to use bio-identical hormones and look at estrogen, they have to be checking serotonin levels to make sure that the estrogen is going to be effective, or to see how much estrogen the patient really needs. Maybe by boosting serotonin they don't quite need as much estrogen or estradiol, and they can lower their exposure and risk.

Ms. Cowger: Consider the case of a slightly post-menopausal patient who comes to your cardiology practice with a family history of cardiovascular problems, but relatively normal weight. Would you look at doing something like the NeuroCardio panel and then adding in hormone lab work?

Dr. Weiss: Yes, and I'm going to take that a step further. We now know that serotonin is really important. If we don't run serotonin levels as part of a heart panel, within ten years that will be malpractice. The data coming out is unequivocal. Given that healthy estrogen levels maintain vascular linings, and its relationship to serotonin, it's so obvious. Women have been telling us this for a long time, "I don't feel well, and my moods are down." And we dismissed it.

Ms. Cowger: It seems that statistically, at this menopausal crossroad, not only does the cardiovascular incidence rate jump, but we also see a lot of inflammatory conditions arise. We see the fibromyalgia rates spike, we see other inflammatory issues like metabolic syndrome, arthritis, and asthma start to really crop up at mid-life. Yet somehow the cardiovascular piece wasn't factored in all that other literature. It seems like we need to integrate all the different pieces of the puzzle.

Dr. Weiss: We also need to begin treating menopause when women are 40 and 45, to get their bodies ready for the change. When we're looking specifically at women and heart disease, as you pointed out earlier, we need the entire panel: hormones, neurotransmitters, cytokines, ApoB's, myeloperoxidase, and the oxidized LDLs. With women, we always have to go to another level to truly assess health status, especially with the hormones, because they are so complex. Since many women are using bio-identical hormones, they are getting those levels checked every 3-6 months anyway (or they should be to make sure that those levels are safe and accurate). So the women's heart panel is going to have serotonin, but also estradiol, estriol, esterone, progesterone, and DHEA as part of that evaluation. Forewarned with that kind of information, we are in a much more proactive position relative to treatment and prevention.





## Cardio Lab Work

### Tools for Evidence-Based Medicine

Ms. Cowger: So where do you see the NeuroCardio taking cardiovascular disease assessment and management?

Dr. Weiss: I believe the NeuroCardio panel will eventually replace every cardiovascular panel in the world. Beyond that, there is no other place to go but to look at immediate risk and at underlying central nervous system control. There is no place else to go now that we have finally recognized depression as a risk factor for coronary disorders. Clearly we are going to have to assess serotonin and norepinephrine levels. The data is here, and it's overwhelming.

In the past, my success in managing heart disease in thousands of patients required the use of my intuition, but the NeuroCardio panel takes the guesswork out of medicine. Now when I see a low serotonin level, I can target that with 5-HTP. I can target methylation issues. I can target high cytokines using natural botanical anti-inflammatories or lifestyle. I can target oxidized LDL with antioxidants such as alpha lipoic acid and vitamins D, E, and K. The test values enable me to target treatment across all of those parameters.

Throughout our lifespan the parameters change. Our entire body chemistry changes. At 35, patients test one way. All of a sudden at 45 they're coming out of a bad marriage, so I need to consider central nervous system support. And at 55 they're in a good marriage, and they don't need so much of that type of support – but they've gotten fat and stopped exercising, and now I have to look at their inflammation. I can target that very specifically as well. I'll be so much better a doctor.

Ms. Cowger: This NeuroCardio testing casts a fairly wide net. We can start earlier, monitor more effectively, and detect risk factors that we might have missed otherwise. How motivating for patients!

Dr. Weiss: It is completely motivating! And patients get excited. They feel better and their neurotransmitters are better. Compliance goes up. And then they're reporting back to me that they've stopped eating fast food and that going to the salad bar really *is* working. So you have to win patients. You have to win them one at a time, and the NeuroCardio panels allow me to do just that.

*Nancy Faass, MSW, MPH*

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### Case Study: Coronary Heart Failure

Dr. Weiss: Welcome to the office. What can I do for you today?

Patient: I've been told I have congestive heart failure. I had an episode of not being able to breathe at night.

Dr. Weiss: So when you lay down you had a hard time breathing?

Patient: Actually, when I first started to fall asleep I'd stop breathing.

Dr. Weiss: What happens is that the fluid in the lungs is very affected by gravity. Sometimes people feel kind of weak during the day and when they lie down, the fluid starts to move up and they get a drowning effect, like an apnea. Then what happened?

Patient: I was hospitalized for three days, but I didn't present with any of the typical risk factors, so I was released. Four days later I was back with the same condition, and then they kept me there and ran the labs and the echocardiogram and the scans and found that the left ventricle ejection fraction was about half of normal.

Dr. Weiss: Your eight cylinders were down to about four. And some people feel horribly sick at that point; they build up massive amounts of fluid. In your case, you only had one symptom: that odd breathing pattern when you lie down. However, that particular pattern is usually very typical of heart failure; we call it the fluid feathers. You can see it on X-rays that way too. So what happened? You had a hospital course the second time. Did they cath you? Did they echo you?

Patient: Yes, all of it.

Dr. Weiss: And did they find coronary artery disease?

Patient: No coronary artery disease...almost none. The echocardiogram was the only thing that showed the specifics.

Dr. Weiss: So your heart, instead of being shaped like a football, was it shaped like a basketball?

Patient: Like a gigantic pear.

Dr. Weiss: Right, usually these things are caused by viruses, and often it's the coxsackie family of viruses. The walls of the heart are under constant pressure, pushing out, so when the virus attacks those walls and that tissue gets weak, it blows up like a pear or a basketball. But there can be other causes: one is thiamine deficiency or the inability to convert thiamine to the active form, thiamine pyrophosphate. Low selenium can be another factor, and there are other reasons as well. What we probably want to do is consider an overall approach with botanical antivirals, looking at what will modify imperfect cyclic AMP levels, and we can do that with botanicals. And I believe you have a toxic exposure history from what you told me. Paint fumes were a lot of what set this off for you?



## Cardio Lab Work

Patient: Paint fumes made it dangerous. The CHF seemed like it was going to be manageable, but when the paint fumes hit, then it got freaky.

Dr. Weiss: And it will. Your lungs are trying to blow out the fumes, your metabolism is trying to do this, but you require a full pump to do that. Your breath is increasing so your heart has to do more, and it cannot sustain the effort. When the heart starts to struggle that way and there is a little fluid on the lungs, that will irritate the heart, which tends to trigger some electrical problems like ventricle tachycardia.

Patient: I was showing doubles and triples.

Dr. Weiss: It's spooky. You're sick, and you have heart failure. Oddly enough the paint fumes may have saved your life, because if you had not been exposed to those fumes, maybe you wouldn't have gone in that second time or you would have waited another two to three weeks, and then we wouldn't have found out about your weak heart so that we can treat it.

Given your sensitivity to fumes, we might also want to look at systemic gut and liver function to see if we can reduce some of that sensitivity. When I smell paint fumes, I duck and walk away. When you do, it can be devastating. I have seen this kind of sensitivity in dozens and dozens of patients. I have patients that we would isolate for days due to chemical sensitivity. If someone down the hall had perfume on, they would start to react. This is very, very real. That chemical sensitivity comes from the liver and the gut, and those are factors that we can work with. So we not only want to look at the heart, we look at gut and all the other factors that are presenting with these events. We can't just put the heart in a box and treat that in isolation. CHF can be a worse diagnosis than cancer, and I don't know why because my patients have had very encouraging outcomes. I'm not doing rocket science here. I'm giving anti-virals, ubiquinol CO-Q10s, and things like that. We want to get you exercising again, as that ventricle gets down to normal size. I have never had anyone pass on from this. I've never had anybody that needed to go to transplant with this. This is something that I really look forward to working with.

Patient: Great!

### Decker Weiss, NMD, FASA, FFCC

Dr. Weiss became the first naturopathic physician to be board-certified in cardiology, completing non-invasive cardiovascular hospital-based training in the Columbia Hospital system, the Arizona Heart Institute, and the Arizona Heart Hospital. He went on to become a fellow of the American Society of Angiology. For more than a decade, Dr. Weiss maintained privileges at the Arizona Heart Hospital, while opening the Scottsdale Heart Institute, where he has helped thousands of patients reduce or eliminate medication safely as well as eliminate the need for angioplasty, ablation, and bypass surgery by reversing heart disease and managing arrhythmias using naturopathic therapies.

The International Association of Health Care Practitioners and the International Association of Cardiologists named Dr. Weiss, a "Leading Physician in the World" in 2012, a distinction given to fewer than 1,000 physicians each year. Dr. Weiss sits on the Functional Genomics and Translational Biology Committee of the American Heart Association. He currently maintains a teaching-based practice, while shifting the rest of his efforts to intractable conflict resolution as a Senior Fellow and Director for Artis Research's Center for Health and Medicine. His first paper, "*Status of the Central Nervous System during Wartime*," a research study conducted during the latest Hamas-Israeli war, is currently out for comment.

### Christina Cowger, MA, MFT

Ms. Cowger holds an undergraduate degree from Syracuse University, has studied health education at California Institute of Integral Studies, and received her master's degree from Sonoma State University. She has an extensive background in integrative and mind-body medicine, reflecting two decades of research in these fields. A continuing education provider in California for therapists, social workers, and acupuncturists, she has lectured at venues that include California Pacific Medical Center/Sutter Health, Dominican University, Sonoma State University, Women's Association for Addiction Treatment, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and Kaiser Permanente.

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### Editorial

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# Placental Fluorosis: Fluoride and Preeclampsia

by John D. MacArthur

New research and diverse evidence implicate fluoride and fluorosis in the pathogenesis of preeclampsia, the dangerous pregnancy complication caused by the abnormal placenta.

Eclampsia, a convulsive disorder of pregnancy, was described by ancient civilizations of China, Egypt, and India. Late in the 19th century, it was recognized that eclampsia was preceded by new onset hypertension during the second half of pregnancy, hence the term preeclampsia.<sup>1</sup> Increasing since 1980, preeclampsia and related hypertensive disorders of pregnancy affect about 5% to 8% of all births in the US.

Preeclampsia is associated with high maternal and fetal/neonatal morbidity and mortality, especially in developing countries. Each year, preeclampsia is responsible for approximately 18% of all maternal deaths and more than 10,000 infant deaths in the US, whose infant mortality rate is one of the highest in the industrialized world.

The abnormal placenta is the major cause of this life-threatening pregnancy complication. Its removal puts an end to the disease. Despite a long history and extensive research, the cause of preeclampsia remains unknown.

Something else that's been around for millennia is fluoride and fluorosis, the visible evidence of an individual's susceptibility to fluoride's adverse systemic effects, but they have never been associated with preeclampsia ... nor ruled out ... nor considered – even though US fluoride researchers have long known that placentas of women who drink fluoridated water contain significantly higher

concentrations of fluoride. In a 1952 issue of *Science* magazine, Harold C. Hodge (chief toxicologist for the US Army's Manhattan Project) reported that women who drank artificially fluoridated water (1.0–1.2 ppm fluoride) averaged 2.09 ppm fluoride in their placentas, compared with 0.74 ppm fluoride in the placentas of women who drank nonfluoridated water (0.06 ppm fluoride). Maternal blood fluoride levels were also nearly three times higher (0.040 vs. 0.014 ppm) because of fluoridation.<sup>2</sup>

More recent clinical research shows that the placenta can accumulate fluoride in healthy women who are exposed in pregnancy to relatively low fluoride concentrations in water and in air. The placenta acts as a natural barrier to the passage of larger quantities of fluoride to the fetus. Fluoride content of the placenta can be significantly higher than that of maternal serum, while cord blood has the least fluoride.<sup>3,4</sup>

Preeclampsia is a progressive disorder with mild to severe consequences, and epidemiological studies clearly confirm that genetic factors are involved.<sup>5</sup> Dental fluorosis also has mild to severe consequences, and animal studies show that there is a genetic component in the pathogenesis of dental fluorosis and in bone response to fluoride exposure.<sup>6</sup> In humans, severity of dental fluorosis varies individually at the same level of intake.<sup>7</sup> Black children in the US have significantly higher rates and more severe forms of dental fluorosis than either white or Hispanic children. When African American women have preeclampsia, its effects are severe and present earlier than in other races.

Most fluoride research is dental research, especially in English-speaking countries that artificially fluoridate their drinking water. A PubMed search for papers published in 2014 yields 2013 results for *fluoride* and 2687 for *placenta*. A search for *fluoride placenta* yields only 11 results in the past 10 years. One is relevant to preeclampsia, Tskitishvili et al. (See "Angiogenic Factors and Fluoride," below.)

Very little is known about how the human placenta is affected by fluoride's multiple mechanisms of cytotoxicity, but placental fluorosis is certainly a possibility.<sup>8</sup> Like dental fluorosis, a woman's vulnerability to placental fluorosis would depend on individual genetic, metabolic, and environmental factors.

## Endoplasmic Reticulum Stress

This century's science is revealing that preeclampsia and dental fluorosis share the same key subcellular mechanism of pathophysiology: endoplasmic reticulum stress. Within a cell, the endoplasmic reticulum (ER) is the organelle responsible for the biosynthesis, folding, and assembly of all secretory and membrane-bound proteins. ER function is highly sensitive to extracellular stimuli. During environmental, developmental, or genetic stress, the cell's folding capacity can become overwhelmed and cause misfolded proteins to accumulate, a condition known as ER stress.<sup>9,10</sup>

Buhimschi et al. have identified misfolded proteins specific to preeclampsia in the urine of pregnant women, weeks before their preeclampsia becomes clinically apparent.<sup>11</sup> Note: Early in the 20th century, proteinuria was identified

as the second cardinal feature of preeclampsia.<sup>1</sup>

ER stress activates a defense mechanism called the "unfolded protein response" that reduces protein synthesis to decrease the burden on the ER. Cells with high secretory activity, such as blast cells, have a large amount of ER and are more susceptible to ER stress.

### Fluoride Causes ER Stress in Fluorosis

Ameloblasts are cells present during tooth development that secrete large amounts of proteins that later mineralize to form tooth enamel.

Researchers at the Forsyth Institute in Massachusetts, a fluoride research center for the past century, found that fluoride initiates an ER stress response in ameloblasts that interferes with protein synthesis and secretion – culminating in dental fluorosis. Beginning with the lowest dose tested, they observed an increase in the magnitude of ER stress with increasing doses of fluoride.<sup>12</sup>

Osteoblasts are cells that secrete the protein matrix for bone formation. In its comprehensive 2006 report, "Fluoride in Drinking Water," the US National Research Council (NRC) said, "Fluoride is a biologically active ion with demonstrable effects on bone cells, both osteoblasts and osteoclasts."<sup>13</sup> In the pathogenesis of skeletal fluorosis, fluoride causes ER stress during osteoblast maturation.<sup>14</sup>

The area enclosed by the membrane of the ER includes a network of interconnecting flattened saclike structures called *cisternae*. Fluoride has been shown to cause dilated *cisternae* in the brains of rats, as well as in the brain tissue of human fetuses from an endemic fluorosis area.<sup>15,16</sup> In fetuses whose mothers all had dental fluorosis, the major subcellular pathology was varying degrees of cistern dilation in glandular epithelial cells of livers, adrenal glands, and thyroid glands.<sup>17</sup>

### ER Stress in Preeclampsia

Trophoblasts are the precursor cells of the human placenta. The extensive secretory activity of syncytiotrophoblasts, the outer trophoblast layer responsible for

nutrient exchange, renders them vulnerable to ER stress.

At the University of Cambridge's Center for Trophoblast Research, Burton and Yung confirmed high levels of ER stress in placentas from cases of early-onset preeclampsia (<34 weeks' gestation). Reduced protein synthesis caused by ER stress has a severe detrimental effect on placental development by causing decreased levels of many hormones, growth factors, and regulatory proteins – leading to the placental insufficiency and dysfunction of preeclampsia.<sup>18</sup>

ER stress is specific to syncytiotrophoblasts, the cells in direct contact with maternal blood – the source of fluoride exposure. Electron micrographs of syncytiotrophoblasts in the normal placenta show the *cisternae* have only minimal dilation. In preeclamptic placentas, the *cisternae* are widely dilated.<sup>18</sup> The precise cause of ER stress in preeclampsia is not known.

Research into the effects of environmental fluoride pollution on human placentas found a richness of fluoride deposits in the placenta that were approximately proportional to the intensity of the pollution. The primary change was a deterioration of cytochrome c oxidase in the villous syncytiotrophoblast, which consequently resulted in a lack of energy supply and placental insufficiency.<sup>19</sup>

### Vascular Calcification, Fluorosis, and Hypertension

PET/CT scans show that vascular calcification and fluoride uptake are significantly correlated in most arterial walls. In coronary arteries, fluoride uptake is considerably higher in patients with cardiovascular events.<sup>20</sup> A significant positive association was found between excess fluoride exposure from drinking water and prevalence of carotid artery atherosclerosis in adults living in fluoride endemic areas.<sup>21</sup>

In patients with calcific aortic stenosis, the uptake of <sup>18</sup>F-sodium fluoride identifies active tissue calcification and predicts disease progression.<sup>22</sup> The elastic properties

of the ascending aorta are impaired in patients with fluorosis.<sup>23</sup> Aortic stiffness is a marker of cardiovascular disease, including hypertension, the cardinal feature of preeclampsia.

Recent evidence shows that excess fluoride intake from drinking water appears to exert an increase in primary hypertension.<sup>24</sup> Sun et al. showed that with the increase in water fluoride concentrations, the risk of essential hypertension in adults grows in a concentration-dependent manner. With fluoride in water at 0.84 mg/l, the prevalence of hypertension was 20.16%. At 1.55 mg/l, it was 24.54%. At 2.49 mg/l, it was 32.30%.<sup>25</sup>

Preeclampsia serves as a sentinel marker for women who will experience premature cardiovascular and cerebrovascular diseases.<sup>26</sup> Since 1984, more women than men have died each year from heart disease.

Women are also disproportionately affected by arthritis, the leading cause of physical disability. The prevalence rate for arthritis in the US is 33% higher in women than in men.<sup>27</sup> The NRC reported that fluoride is readily incorporated into the crystalline structure of bone and will accumulate over time, which can result in arthritic symptoms of joint stiffness and pain.<sup>28</sup>

### Placental and Pineal Calcification: Melatonin and Fluoride

Placental calcification is associated with a 40-fold increase in the incidence of IUGR, (intrauterine growth restriction), which is also a consequence of placental insufficiency. In cases of IUGR complicated by preeclampsia, placental infarcts in the third trimester were significantly increased.<sup>29</sup>

Fluoride concentrations in the water of most tissues are 40% to 90% of plasma concentrations but can exceed 100% in tissues with calcium deposits, such as the placenta late in pregnancy.<sup>30</sup> Chlubek et al. found a high positive correlation between fluoride and calcium concentrations in the placenta.<sup>3</sup>

Calcium is the nutritional supplement found most effective in the prevention of preeclampsia.<sup>1</sup> As an antidote to fluoride poisoning, calcium

## Placental Fluorosis

is used to reduce absorption and enhance excretion of fluoride.<sup>31</sup>

"As with other calcifying tissues, the pineal gland can accumulate fluoride... with the fluoride concentrations being positively related to the calcium concentrations in the pineal gland," said the NRC. "Fluoride is likely to cause decreased melatonin production."<sup>32</sup>

Melatonin is essential for proper trophoblastic function and development.<sup>33</sup> Decreased maternal blood levels of melatonin are found in preeclamptic compared with normal pregnancies. Lanoix et al. have shown that the human placenta produces melatonin and expresses its receptors. In preeclamptic placentas, the researchers found a significant inhibition of melatonin's rate-limiting enzyme that correlated with decreased melatonin levels.<sup>34</sup>

### Oxidative Stress: Fluoride, Melatonin, Acetaminophen

Preeclamptic placentas exhibit a greater extent of both ER stress and oxidative stress.<sup>35</sup> Oxidative stress is a recognized mode of fluoride toxicity that has been observed in several types of cells and also in different organ systems in animals and in people living in areas of endemic fluorosis.<sup>36</sup> Increasing oxidative stress in children with fluorosis is associated with increasing fluoride concentration in their drinking water.<sup>31</sup>

Melatonin has ameliorated oxidative damage to the placenta and to the fetus in experiments using nonhuman mammals.<sup>37</sup> Animal research confirms that melatonin can upregulate the antioxidant defense system impaired by fluoride-induced oxidative stress in the liver, heart, and kidney of female rats.<sup>38</sup>

Melatonin has been referred to as a "suicidal" antioxidant. Once oxidized, it cannot be reduced to its former state.<sup>39</sup> By reacting with fluoride, the melatonin available to the placenta is reduced.

Acetaminophen, the medication most commonly used by pregnant

women for fevers and pain, is associated with an increased risk of preeclampsia when taken during the third trimester.<sup>40</sup> Acetaminophen can cause oxidative stress, even at low doses, but co-exposure with fluoride has a synergistic effect.<sup>41</sup> Together, acetaminophen and fluoride (in subtoxic doses) enhance oxidative stress and kidney damage in rats, as compared with rats treated only with fluoride or with acetaminophen. Acetaminophen also significantly decreases urinary fluoride excretion, which is how the body rids itself of previously absorbed fluoride.<sup>42</sup>

Note: Rodent studies are relevant to humans, because a much higher concentration of fluoride is required to cause dental fluorosis in a mouse than in a human (25 vs. 2 ppm).<sup>12</sup>

### Angiogenic Factors and Fluoride

During mid-gestation, the maternal uterine spiral arteries must be transformed into low-resistance, high-capacitance blood vessels that can provide increasing amounts of oxygen and nutrients to the growing fetus. Poor spiral artery remodeling due to an abnormal balance of proangiogenic and antiangiogenic factors causes the hypertension seen in preeclampsia.

The fetus secretes adrenomedullin, a proangiogenic vasodilator, into the placenta. In normal human pregnancies, adrenomedullin is elevated approximately 5-fold in the maternal plasma, but often blunted in pregnancies complicated by preeclampsia.<sup>43</sup> Sodium fluoride has been shown to completely block the effect of adrenomedullin in pregnant rats.<sup>44</sup>

Fetal fluoride levels in blood and amniotic fluid depend on maternal fluoride exposure. The use of fluoride supplements (1.5 mg/day) doubles fetal blood concentrations.<sup>7</sup> When pregnant women consume 1.25 mg of fluoride per day, the fluoride concentration in their amniotic fluid is significantly higher than in women who consume 0.25 to 1.0 mg fluoride.<sup>45</sup> Fluoride levels in amniotic fluid – which are considerably higher at term than earlier in the third trimester – are positively correlated in a dose-response relationship with fluoride content and pathology of fetal bones,

with significantly greater fluoride levels in fetuses born to mothers who have dental fluorosis.<sup>46,47</sup>

Soluble endoglin (sEng) is an antiangiogenic protein whose concentrations are elevated in serum and in amniotic fluid of women with preeclampsia.<sup>48</sup> Tskitishvili et al. found that amniotic tissue cultures treated with sodium fluoride show significantly higher expression levels of sEng, at any dose and time-point tested.<sup>49</sup>

### Inflammation: Periodontal Disease, Preeclampsia, and Dental Fluorosis

Maternal periodontal disease with systemic inflammation as measured by hs-CRP (high-sensitivity C-reactive protein) is increased in preeclampsia and represents a marker of its severity.<sup>50,51</sup> Women with a history of periodontal treatment are more likely to develop severe preeclampsia than women without a prior history of treatment.<sup>52</sup> Periodontal treatment exposes women to extremely high concentrations of topical fluoride (22,600 ppm), some of which is absorbed into the bloodstream and placenta.

Plasma levels of hs-CRP are significantly higher among patients with fluorosis compared with controls.<sup>53</sup> A clinical study found a strong association of occurrence of periodontal disease in people who had dental fluorosis. As the severity of fluorosis increased, periodontitis increased from 8.5% to 35.8%. Also, periodontitis was significantly more common in females.<sup>54</sup> Many studies and published documents have shown that increased fluoride exposure is directly linked to increased periodontal disease.<sup>55</sup>

Preeclamptic women with periodontal disease are at greater risk for preterm delivery.<sup>56</sup> Maternal fluoride consumption is also a risk factor for preterm birth, a leading cause of long-term neurological disabilities in children. The societal economic burden associated with preterm birth is more than \$25 billion per year in the US.<sup>57</sup> Preeclampsia is the underlying cause of about 25% of all medically indicated preterm deliveries.

Another pro-inflammatory factor in preeclampsia is elevated liver

enzymes, which are significantly higher in early-onset preeclampsia.<sup>58</sup> Elevated liver enzymes have been found in children, based on the levels of fluoride in drinking water (in a dose-response manner) and on their degree of dental fluorosis.<sup>59</sup>

### Fluoridated Water, Dental Fluorosis, and Preeclampsia

A case-control study found a significant association between fluoride levels in drinking water, dental fluorosis in mothers, and low birth weight of newborns. Preeclampsia was significantly associated with low birth weight (23.1% in cases vs. 11.6% in controls).<sup>60</sup>

Systemic exposure to fluoride through drinking water is associated with an increased risk of dental and bone fluorosis in a dose-response manner – without a detectable threshold.<sup>61</sup> British researchers estimate the prevalence of dental fluorosis of all levels of severity to be 15% in nonfluoridated areas and 48% in fluoridated areas.<sup>62</sup>

From 1987 to 2004 in the US, the prevalence of moderate and severe dental fluorosis nearly tripled from 1.3% to 3.6%.<sup>63</sup> There was also a 13.5% increase in the percentage of Americans receiving public water that was fluoridated (from 60.5% to 68.7%).<sup>64</sup>

During the same 18 years in the US, the incidence rate of preeclampsia rose by 25%: from 23.6 to 29.4 cases per 1000 deliveries.<sup>65</sup> Rates of severe preeclampsia are steadily increasing. In the largest US cohort study (120 million births), the prevalence rate for severe preeclampsia nearly quintupled from 0.3% in 1980 to 1.4% in 2010.<sup>26</sup>

The limited available population data reveal that, from 1996 to 2004 the preeclampsia rate averaged 19% higher in the two most fluoridated regions of the US (South and Northeast), than in the two least fluoridated regions (Midwest and West): 31.7 vs. 26.6 cases per 1000 deliveries. The preeclampsia rate averaged 40% higher in the South than in the West: 34.1 vs. 24.3 cases per 1000 deliveries.<sup>65</sup> In 2004, the average fluoridation rate in the South's 16 states was 81%, compared with 46% in the West's 13 states.

Note: The age-adjusted death rate in 2010 for essential hypertension and hypertensive renal disease was 9% higher in the 22 states fluoridated at 80% or more (average 92%) than in the 27 states fluoridated at less than 80% (average 56%).<sup>66</sup>

### Fluoridated Water, Hypothyroidism, and Preeclampsia

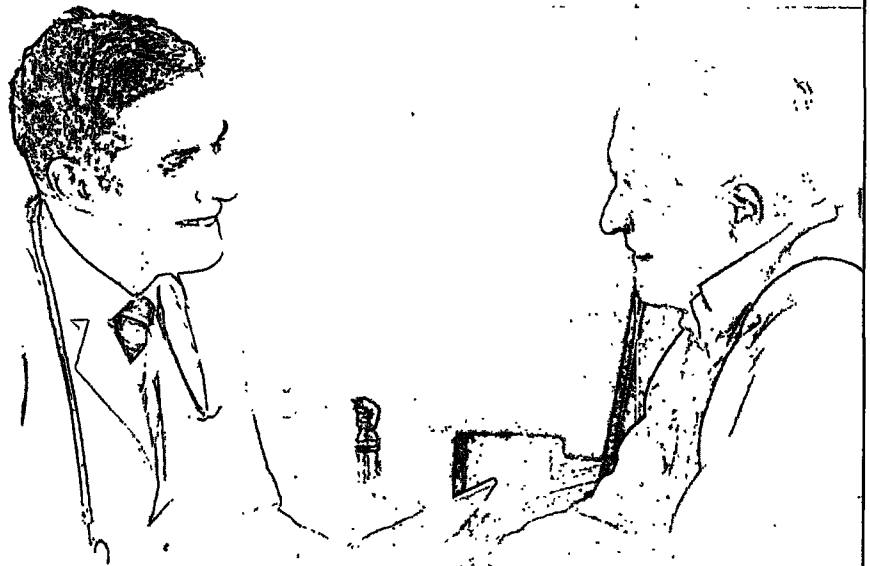
In 2015, a major population-level study analyzed data from

## Placental Fluorosis

99% of England's 8020 general medical practices. It found a positive association between fluoride levels in water and patients diagnosed with hypothyroidism. High hypothyroidism prevalence was 30% more likely in practices located in areas with fluoride levels in excess of 0.3 mg/l. Those

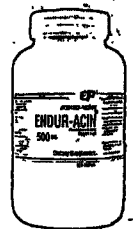


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## Placental Fluorosis

located in the West Midlands (a wholly fluoridated area) were nearly twice as likely to report high hypothyroidism prevalence in comparison with Greater Manchester (nonfluoridated area).<sup>67</sup> The study did not include undiagnosed subclinical hypothyroidism, which is associated with many health problems, including preeclampsia and ADHD.

Preeclampsia is often complicated with subclinical hypothyroidism. Many studies have shown a relation between the level of thyroid hormones and development and severity of preeclampsia.<sup>68</sup> In an analysis of pregnancy outcomes in 24,883 women, after adjusting for confounding factors, there was a significant association between subclinical hypothyroidism and severe preeclampsia.<sup>69</sup> A 2013 retrospective cohort study of 223,512 pregnancies found that primary hypothyroidism was associated with increased odds of preeclampsia (OR = 1.47).<sup>70</sup>

Singh et al. tested drinking water and body fluids for fluoride content, plus thyroid hormone and TSH levels, in children with dental fluorosis. They observed that high fluoride exposure can cause functional abnormalities of the thyroid. "Different degrees of dental fluorosis could be observed, with significant deviation in the serum thyroid hormone levels."<sup>71</sup> Note: ER stress has been detected in the thyroid glands of fetuses whose mothers had dental fluorosis.<sup>17</sup>

Hypothyroidism is associated with ADHD and is considered a potential cause of the disorder. Also published in 2015 was the first population-based study to examine the relationship between exposure to fluoridated water and ADHD prevalence. A multivariate regression analysis showed that artificial water fluoridation prevalence was significantly positively associated with ADHD prevalence. After socioeconomic status was controlled, each 1% increase in artificial fluoridation prevalence in 1992 was associated with approximately 67,000 to 131,000 additional ADHD

diagnoses from 2003 to 2011 in the US.<sup>72</sup>

### FDA: Fluoride and Pregnancy

The FDA classifies fluoride as an unapproved drug in Pregnancy Category C: "Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans." The FDA says that a drug in category C "may pose risks similar to a drug in Category X," which carries the warning: "The risks involved in use of the drug in pregnant women clearly outweigh potential benefits."<sup>73</sup>

As for any potential benefits of swallowing fluoride, after reviewing the best available evidence for the effectiveness of water fluoridation, the FDA would only allow a weak claim: "Drinking fluoridated water may reduce the risk of tooth decay" – a far cry from the inflated sales pitch of fluoridation promoters.<sup>74,75</sup>

Since 1966, the FDA has prohibited claims that prenatal fluoride supplements benefit the teeth of children.<sup>76</sup>

Fluoride is added to the drinking water of more than 200 million Americans. This EPA-regulated water contaminant now pervades the nation's processed-food-and-beverage-chain, essentially making the US artificially fluoride endemic.

The actual amount of fluoride that pregnant women typically consume per day is unknown.

### Research Needed

To begin with, measure fluoride levels in routine blood and urine tests. For women who previously experienced preeclampsia, determine if their drinking water was fluoridated. Did they regularly drink tea or beverages manufactured with fluoridated water? How severe was their preeclampsia? Do they have dental fluorosis, a biomarker of their genetic susceptibility to fluoride?

A next step is to compare the concentration of fluoride in preeclamptic placentas with the severity of preeclampsia, as well as with placentas from normal pregnancies.

### Preventing Preeclampsia

Preeclampsia used to be called "toxemia," until 20th-century science failed to identify the causative substance. The current name *preeclampsia* (preconvulsions) continues to reflect our failure to determine the etiology of this life-threatening disease of the placenta. This century's science suggests that "placental fluorosis" may be a far more accurate term.

Bottom line: Not ingesting fluoride poses absolutely no risk (or lack of benefit) to the placenta or fetus; however, consumption of fluoride may very well increase a woman's risk of preeclampsia and its dangerous short-term and lifelong consequences for her and her child.

Women who are pregnant (or intend to be) should not swallow fluoride in supplements, in dental products, or during dental procedures. They should not consume fluoridated water or beverages manufactured with it.

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John D. MacArthur's previous contributions to the *Townsend Letter* include three reports in October and November 2013: "Too Much Copper, Too Little Zinc, and Cognitive Deterioration in Alzheimer's Disease" (with George J. Brewer, MD), "Fluoride and Preterm Birth," and "Overdosed: Fluoride, Copper, and Alzheimer's Disease."



# Neural Prolotherapy: An Effective Pain Therapy

by Jeff Harris, ND

Neural prolotherapy (NPT) is a simple and very effective treatment for pain. It uses injection of sugar near cutaneous nerves to extinguish neurogenic pain and neurogenic inflammation. Science has found some of the reasons for the profound effects of sugar or sugar alcohols in these injections, but there is still more to be researched at this time. Nonetheless, NPT is so safe that it is worth a try in all pain conditions.

It has been found that NPT resolves 80% of all pain, as 80% of all pain is neuropathic or from neurogenic inflammation – meaning that the nerves become damaged and send a pain signal and cause inflammation.

The definition of neuropathic pain by Professor Douglas Zochodne states that it is: “a severe and debilitating pain that can render patients unable to walk, work, sleep or enjoy life. ... Full and effective regeneration of the peripheral nervous system usually extinguishes this pain.”<sup>1</sup> John Lyftogt, MD, of Christchurch, New Zealand, has researched and developed the science of identifying and treating neuropathic pain and neurogenic inflammation with injections of 5% dextrose (D5W) or mannitol (M5W) near the damaged or inflamed nerves. This extinguishes the pain and inflammation immediately and is diagnostic for neuropathic pain and neurogenic inflammation.

Lyftogt says that he first tried dextrose on his own chronic pains from injury. He was so impressed with the relief that he told his wife, and she volunteered her painful areas and had relief as well. After many successful treatments, he brought it into his practice. One of the first patients was a long-distance runner with debilitating Achilles tendonitis. In this case, Lyftogt treated the lateral sural nerve and lower saphenous nerve where they cross over the Achilles tendon with D5W. The patient was immediately out of pain. Having been unable to train for some time and now feeling better, the patient, like any devoted athlete, promptly went out and ran a 10K. When Lyftogt discovered this, he was surprised and intrigued that the running did not cause a relapse of the tendonitis. He recognized that the treatment had therapeutic value beyond pain relief, and he has since laid out the science and treatment of neuropathic pain. His patients were predominantly amateur and professional athletes with painful injuries, and with the treatment of their cutaneous nerves, he found that they got pain relief and could continue to train, because the injury (the damaged nerve) was healed. Lyftogt has learned that neurogenic inflammation can advance and

worsen over time, so the sooner the original injury is treated, the fewer treatments are needed for complete healing.

The science of NPT developed by Lyftogt lays out the function and dysfunction of nerves when they are damaged. Neurogenic pain is caused by damage to the C fibers of cutaneous nerves. C fibers are unmyelinated nerves, about 1 micron in size, of low conduction velocity. In other words, they send a slow signal compared with other nerves. They were discovered in the 1960s with the invention of the electron microscope which allowed them to be visualized. C fiber nerves are afferent and efferent, which helps explain the complexity of experience of neurogenic pain. There is a receptor on the nerves called TRPV1 (transient receptor potential cation channel, subfamily V [vanilloid], member 1), whose previous name was the capsaicin receptor. TRPV1 is regarded as the central nerve receptor in initiating and maintaining pain-related behaviour in animals and pain experience in humans.<sup>2</sup> They are responsible for the burning sensation often described in pain syndromes.<sup>3</sup> For a direct experience of the burning pain by a TRPV1 receptor and its treatment using the principles of NPT, eat a hot chili pepper and then take a sip of a sugary drink and hold it in your mouth. You will find that the burning sensation is extinguished because the sugar changes the signal from the TRPV1 receptors in the nerves of your mouth. This is proposed to be the effect that is happening with the injections of dextrose.

TRPV1 is the principle mediator of:

- tissue maintenance and renewal
- inflammation and neuropathic pain
- pain with disease and degeneration

The TRPV1 receptors are activated by:

- noxious stimuli
- high temperatures
- pressure (greater than 30 mm Hg)

These stimuli cause the nerve to convey a pain/inflammation message to the central nervous system. It only takes pressure of 30 mm Hg or greater to compress the nerve enough to cause the pain. What happens is that the cutaneous nerves passes through the fascia into the subcutaneous space from deeper tissue. As the nerve passes through openings, these can be restrictive or the nerve can be



swollen so that it is restricted. This causes compression of the nerve, and the nerve compression and subsequent damage is called a chronic constriction injury (CCI).<sup>4</sup> CCIs can be palpated and occur by restriction of the fascia, entrapment in facial ligatures, or entrapment in scar tissue creating a scar neuroma. Exercise causes nerves to swell and become entrapped in these restricted areas either by adhesion or natural ligatures. Commonly a swollen nerve is restricted by a fascial opening, the myelin sheath, and can be stripped with movement or stretching, causing an intussusception injury, which is much like stripping the plastic cover off a wire – very painful for the patient.

For example, a common CCI results in low back pain. There is an osteofibrous tunnel, located 7 to 8 cm laterally from the midline of the spine on the posterior ileum. The affected nerve is the superior cluneal nerve and is from the L1, L2, or L3 nerve root. When a person bends forward the nerve stretches and should normally easily slide through the tunnel, but if the nerve is swollen, it gets caught in the fascial opening and adhesion (CCI), causing stripping and bunching of the myelin sheath with nerve tissue. This is an intussusception injury of the nerve. Patients with this type of nerve injury reports that their backs went out on them. They go for an exam and are usually diagnosed with a disc injury at L4–5 or L5–S1, a fairly common condition in people over 40 years old that doesn't usually cause pain. The patient is prescribed back rest, the nerve swelling recedes, the nerve remyelinates, and the pain goes away. Or the patient goes for surgery and has some or no relief because the cause of the nerve injury is not addressed by the surgery.

As the intussusception injury is repeated, the bunched-up nerve and sheath build up on one or both sides of the tunnel and enlarge over time. Patients call these palpable lumps their "marbles" or "back mice"; also they have had them diagnosed as lipomas with nerve infiltration. NPT is the ideal treatment for this type of low-back pain. The injection

of D5W to the osteofibrous tunnel entrances and along the nerve course immediately relieves pain and improves range of motion. The patient is amazed and frequently has a confused look on his face due to the sudden absence of pain with movements that used to always be excruciating. Lyftogt states that the diagnostic criterion for neurogenic pain is if the pain goes away with treatment, then it's neurogenic in origin.

Neurogenic inflammatory signals and pain signals are sent by the release of calcitonin gene-related peptide (CGRP) and substance P (SP).

These are documented effects of CGRP from Susan Brain in 1985:

- vasodilator of precapillary arterioles
- enhances the vascular permeability and protein extravasation effect of SP
- upregulation of VEGF causing neovascularisation and neurogenesis. VEGF increases MMP1 leading to collagenolysis (degeneration of tendons)
- increased tissue calcium levels (calcifications)
- stimulation of osteoclasts (dystrophy bone, stress fractures)

The documented effects of SP include:

- vasodilator of postcapillary venules which cause increased vascular permeability in postcapillary venules, leading to protein extravasation (tissue edema)
- chemoattractive to immune cells
- SP in a positive feedback loop is an important regulator of the immune system. Activates immune cells to produce cytokines
- binds to mast cells, causing degranulation
- affects the amygdala, causing depression
- stimulates CRH release in the hypothalamus, upregulating the HPA stress response. Prolonged activation may lead to exhaustion (DHEA depletion)

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- How to diagnose neuropathic pain
- How to treat neuropathic pain with subcutaneous near-nerve injections with dextrose 5% in sterile water

Dr Lyftogt has published seven papers in the *Australasian Journal of Musculoskeletal Medicine* and is co-author of a Randomised Control Trial on the treatment of Achilles Tendinitis (*The British Journal of Sports Medicine*, June 2009 and April 2011). His website is: [www.doctorlyftoff.co.nz](http://www.doctorlyftoff.co.nz)

To sign up for the workshop or ask questions you can contact Jeff Harris, ND, 206-517-4748 and get more details from his website: [www.jeffharrisnd.com](http://www.jeffharrisnd.com)

# Neural Prolotherapy

- sensitizes peptidergic nociceptors, leading to neuropathic pain with allodynia and hyperalgesia
- impairs proprioception by delaying antagonist muscle reflex inhibition (neurogenic inflammation of MEP)
- causes increased intramuscular compartment pressure

It is interesting that the same TRPV1 receptors in the C fibers also send a healing signal through the release of somatostatin and galanin, which are anti-inflammatory and reverse the effects of the CGRP and SP. This mechanism has not been studied as much as the devastating effects of CGRP and SP.

The TRPV1 receptor is actively being researched to understand its properties, and in a recent German study it was found that the TRP channel polymorphisms contributed significantly to somatosensory abnormalities of neuropathic pain patients. The shape of the pore determines the neuropathic pain potential more than the TRPV1 itself. The pain patients in the study had a much higher frequency of the polymorphism than the healthy controls.<sup>5</sup> It is hypothesized that 20% to 40% of the US population have these polymorphisms that cause the slower healing response, with the result's being neurogenic pain and inflammation.

What a doctor and patient can expect after an NPT treatment is for 4 hours to 4 days to have complete relief of the pain, then to have improvement of the pain each time the pain returns after the 4 hours to 4 days. This means that if the pain is a 10 out of 10, the expectation is that by the next treatment the pain will be an 8 or 9. With single-area pain syndromes, I expect complete resolution of pain after five to eight treatment sessions. There can be times during the treatment that the pain doesn't follow the direct descent, but that is not a sign of ineffectiveness of the treatment, and usually after the next visit the descent of pain continues.

There is an art and science to using NPT. While it can be figured out on one's own, the trainings that Lyftogt provides speeds the practitioner to the most effective ways to treat any pain condition. NPT is simple and beautiful; in the way a spiritual truth can be, the deeper you dive into it, the more profound and simple it is. The science and technique of NPT have now been taught all over the world (NZ, US, Canada, Mexico, Italy, Australia, and Netherlands) to more than 400 doctors. Lyftogt is writing a book that covers all the topics of NPT and hopes to be finished this year.

NPT is easily the most important advance in pain treatment and diagnosis in a long time. It has the potential to become the standard for treatment for pain syndromes in physician's offices, pain clinics, and emergency rooms.

## Notes

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5. Binder A et al. Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. *PLoS One*. March 2011;6(3):e17387.

## For Further Reading

For an excellent historical treatment of peripheral nerve injuries, see *Injuries of Nerves and Their Consequences* (Philadelphia: J. B. Lippincott; 1872), by American neurologist Silas Weir Mitchell (1829-1914).

Jeff Harris, ND, is a 1992 graduate of Bastyr University. He teaches neural therapy workshops internationally and also teaches medical procedures at Bastyr University. He practices in Greenlake area of Seattle, Washington. For information on workshops and seminars on neural therapy and neural prolotherapy, see his website: [www.jeffharrisnd.com](http://www.jeffharrisnd.com).



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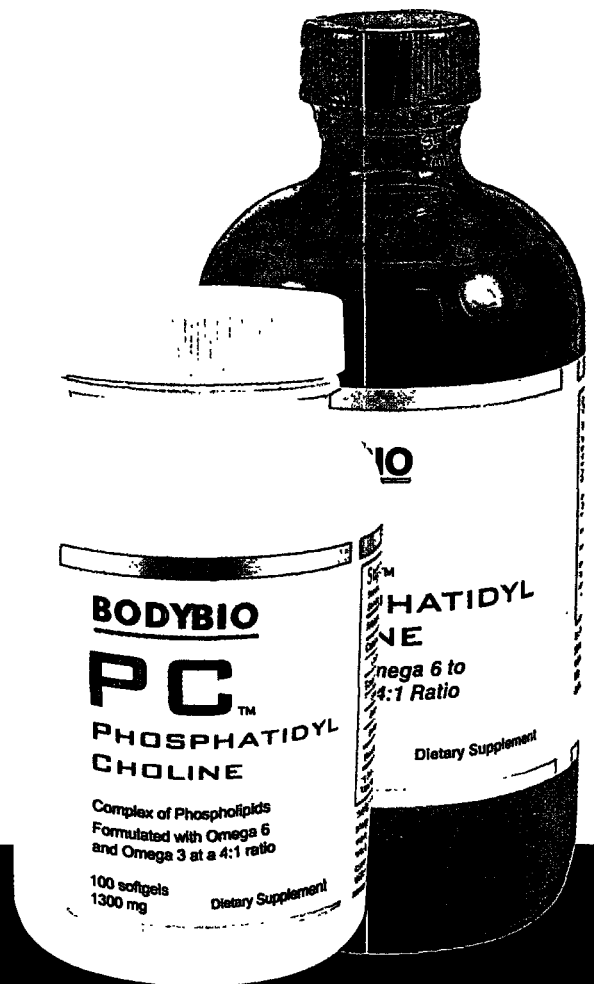


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# FCT Documented Case of an Apparently Reversed Heart Disease in a Junk-Food Addict with Obesity Diabetes, Thanks to Cause-Based Approach to Chronic Diseases

by Savely Yurkovsky, MD

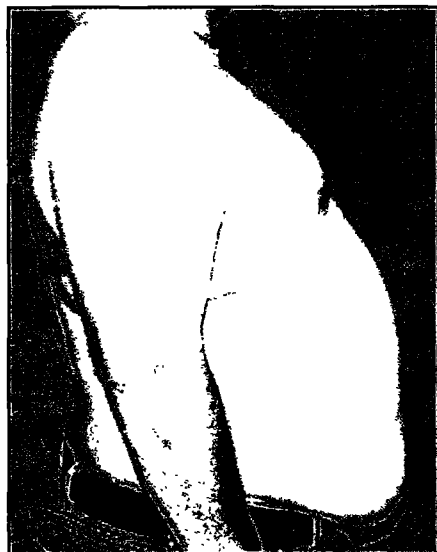


Photo of the patient's state of obesity

A 38-year-old nonsmoking and mildly overweight male sustained documented myocardial infarction in a hospital in December 2002. He had family risk factors for coronary artery disease and was very partial to sodas and other junk food; but outside of the event, no other medical conditions were present at the time. One month following his hospital discharge, his nuclear exercise stress test was consistent with both the suffered myocardial infarction and compromised blood supply, to

another area of the heart, with the latter placing him at risk of another infarction. The report read:

#### Conclusions: (1/28/03)

4. Rare PVCs were present
6. SPECT myocardial perfusion imaging was mildly abnormal with:
  - evidence for mild ischemia involving the basal anterior wall
  - evidence for small infarction involving the apex

Not surprisingly, during the stress test, he developed chest pain, shortness of breath, dizziness, excessive sweating, and abnormal heartbeats (PVCs).

#### FCT Bioresonance Testing and Prescribed Treatment

Bioresonance testing indicated the presence of mercury and residues of tobacco smoke (he grew up in a smokers' home) in his coronary arteries; several other organs tested as energetically impaired. Only homeopathic treatment was administered according to Field Control Therapy's unique causative homeopathic and organ restoration

system. The patient refused to discontinue his junk food diet, due to a strenuous work schedule. Only a few more evaluations with FCT bioresonance testing and the corresponding homeopathic treatments were administered.

Following these, and after bioresonance testing indicated that his coronary arteries were free of any morbid agents, he was referred to repeat his nuclear exercise stress test that he did only 12 months following the myocardial infarction and 11 months following the abnormal stress test.

The results of the repeated nuclear stress test:

#### Myocardial Perfusion SPECT Imaging: (12/17/03)

##### Impression:

1. No evidence of any significant fixed or reversible perfusion abnormality to suggest the presence of an infarct/scar or ischemia.
  2. Normal wall motion with a 52% calculated ejection fraction.
- Correlation with the concurrent stress EKG and the patient's clinical history is suggested for further evaluation.

continued on page 86 ►

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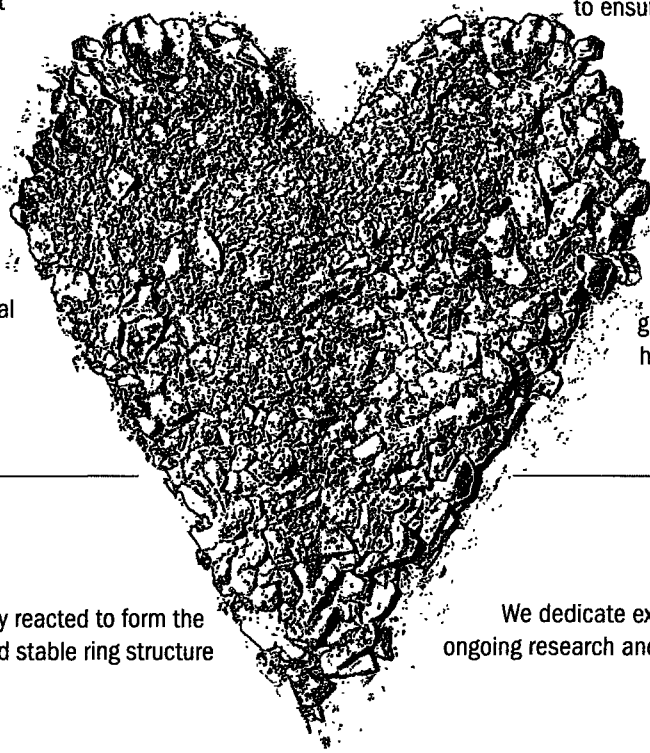
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# Cause-Based Approach to Chronic Diseases

► continued from page 84

His exercise stress EKG part was completely normal this time, without his having any chest pain or other symptoms.

## Further Heart and Overall Medical Course Since

For the next 10 years, the patient's intake of junk food skyrocketed, due to his addiction and pace of life in working two full-time jobs. This was compounded by severe deficiency in rest and even sleep, as he also worked nights. As a result, his weight ballooned by some 120 pounds above the norm, with diabetes, hypertension, fatigue, brain fog, depression, anxiety, rage, severe memory problems, and periodic recurrence of chest pains following suit. Adding high triglycerides to his diabetes due to insulin resistance and obesity also earned him another

unpleasant medical label known as metabolic syndrome.

Yet he refused to curb his consumption of junk foods and never took any other treatments, or even supplements, besides carrying out just a few and sporadic FCT sessions a year. Following these, which were addressing his ongoing mercury problem (no money to remove mercury fillings), parasites, candidiasis, viruses, dysbacteria, all lodged in many organs (including the brain), he would happily report abolition of all of his symptoms, and vanish for months while maintaining his self-destructive lifestyle.

However, during one of these long periods of vanishing, his condition seemed to reach its critical stage. Sometime in early 2012, he was seen for severe bouts of angina by a local cardiologist at the well-known

Heart Center of St. Francis Hospital on Long Island. He refused cardiac catheterization for fear of having to face the necessity of a coronary bypass surgery, because the CT scan of his heart did indicate a blockage in one of the most strategic heart arteries. He returned to FCT months later, being almost 50 at the time, mainly because of the pain in his testicles, excessive anger for months, and recent bouts of chest pain.

## FCT Bioresonance Testing and Treatment

Mercury and other heavy metals and other environmental pollutants were in the patient's testicles and coronary arteries, with some of these in the brain and organs of the immune and endocrine systems, as well as excessive EMF. He was offered the EMF-protective technology Memon,

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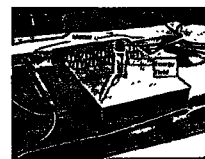


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# Cause-Based Approach to Chronic Diseases

and the corresponding homeopathic treatment. He soon reported resolution of these complaints. Yet 2 months later he was admitted on an emergency basis to the same heart center with severe chest pains and uncontrolled diabetes, necessitating heart and insulin treatments.

This time he did agree to and underwent cardiac catheterization. However, in spite of his prior heart history along with other overwhelming cardiac risk factors, the report of his heart or coronary arteries read the following:

**Coronary angiography was performed in multiple views and revealed: (7/1/13)**

Left main coronary artery was unremarkable.

The left anterior descending was remarkable.

The circumflex was unremarkable.

The right coronary artery was the dominant vessel.

Right coronary artery was unremarkable.

The cardiologists there could not explain or control his chest pain, and he was back to FCT.

## FCT Bioresonance Testing and Treatment

Lyme bacteria and flu virus were lodged in his heart muscle, and Lyme was also found in the brain. Only homeopathic and a short course of treatment was administered, which promptly abolished the pain.

Savely Yurkovsky, MD, graduated from II Moscow State Medical Institute in 1975 with a degree in pediatric medicine. He completed his training in internal medicine and cardiology at Coney Island Hospital of Downstate Medical School, and is board certified in internal medicine. He has been in private practice since 1984 with a special focus on identifying and successfully treating the main causes of chronic diseases via bioenergetic modalities – bioresonance testing and homeopathy, correspondingly, or FCT.

Dr. Yurkovsky has founded a teaching organization, SYY Integrated Health Systems Ltd., dedicated to training in FCT. It had been presented extensively in the US and Europe to medical practitioners since 1999, and has demonstrated numerous documented reversals in a variety of chronic diseases.

His book, *The Power of Digital Medicine*, was endorsed for scientific validity by two prominent physicists: MIT Professor George Pugh, PhD, and the former chairman of materials science at Stanford University, Professor William Tiller, PhD, as well as by Mehmet Oz, MD, from Columbia University Medical School. Its diagnostic and homeopathic aspects were also presented at the annual BTR conference, in 2005: Unified Science & Technology for Reducing Biological Threats & Countering Terrorism, affiliated with the Department of Homeland Security and the US Army, as well as at the Department of Psychiatry of Massachusetts General Hospital, Harvard Medical School, and many other professional symposia.

In collaboration with the Department of Gastroenterology of Johns Hopkins University School of Medicine, Dr. Yurkovsky has contributed a chapter on homeopathy to the textbook *Integrative Gastroenterology* (Oxford University Press; 2011) and authored numerous articles on different medical topics.

His book in progress explains the inevitability of the current epidemics of autism, and numerous other brain and somatic diseases and how to solve them.

Contacts for health practitioners' training can be made through information provided in the FCT advertisement on page 85.

## Conclusion

The shortest way to Rome, or to any destination, will always be by a straight line. The shortest way to solve or prevent the great majority of chronic diseases is only through going straight to afflicted organs and properly identifying and addressing their genuine causes of dysfunction. Anything else seems to be just some interesting medical actions merely for disease labels. ♦



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# Roman Horror-Day: Organic Standards Take a Beating at Codex

by Scott C. Tips, JD

As with life, words have plain meanings. That is, we all generally expect the basic meaning of a word to be what we know it to be through our experience and education. A cat does not mean a *dog*. Instead, they are what we expect them to be just as *water* is water and *blue* means blue. Without such commonly accepted meanings, we would be lost at sea, unable to communicate with one another and transmit information. Hence, shared definitions exist that typically transcend time and even cultures.

Yet words can also deceive us, especially if the plain meaning that we expect to be there is not there. More than 200 years ago, the French moralist Joseph Joubert observed that “words, like eyeglasses, blur everything that they do not make clearer.” That is exactly what is happening with the word *organic* as its meaning is changed by those authorities we would think would be the most diligent in safeguarding it.

## What is Organic?

To most of us, “organic” food has a plain meaning. It means food that our grandparents or great-grandparents ate when they were young: natural and free of pesticides and other toxins and contaminants, and certainly not genetically modified! But, today, *organic* has been given a regulatory definition.

The original regulatory definition in the US arose from the Organic Foods Production Act, part of the 1990 Farm Bill. Among other things, this act sought to create uniform national standards and certification for the production and distribution of “organic” foods through a USDA

National Organic Program (NOP). Producers meeting NOP’s organic standards (read, definition) are legally permitted to label their products as “USDA Certified Organic.”

The USDA National Organic Program defines organic production as, “A production system that is managed in accordance with the Act and regulations in this part to respond to site-specific conditions by integrating cultural, biological, and mechanical practices that foster cycling of resources, promote ecological balance, and conserve biodiversity.”<sup>1</sup>

That’s concise, but not too useful as a working definition. So, the USDA’s Consumer Brochure attempts to fill the definitional gap when it elaborates, “What is organic food? Organic food is produced by farmers who emphasize the use of renewable resources and the conservation of soil and water to enhance environmental quality for future generations. Organic meat, poultry, eggs, and dairy products come from animals that are given no antibiotics or growth hormones. Organic food is produced without using most conventional pesticides; fertilizers made with synthetic ingredients or sewage sludge; bioengineering; or ionizing radiation. Before a product can be labeled ‘organic,’ a Government-approved certifier inspects the farm where the food is grown to make sure the farmer is following all the rules necessary to meet USDA organic standards. Companies that handle or process organic food before it gets to your local supermarket or restaurant must be certified, too.”<sup>2</sup> (Note, for the moment, the exceptions built into the definition.)

In the European Union, organic is defined more stringently – but no more clearly – through its 2007 legislation, which states in pertinent part, “‘organic production’ means the use of the production method compliant with the rules established in this Regulation, at all stages of production, preparation and distribution” ... “‘organic’ means coming from or related to organic production.” (emphasis added)<sup>3,4</sup>

Other jurisdictions establish similar wiggle room, wherein *organic* does not mean 100% organic. In the US, this wiggle room was expanded in 2008 when the Department of Agriculture changed the definition to mean that organic products must have at least 95% organically produced ingredients, but that 5% could be nonorganic (including factory-farmed intestines, mercury, and other contaminants).<sup>4</sup> So, unless the product is declared “100% Organic” on its label, it is not really completely organic at all.

## And This Has What Exactly to Do With Codex?

As our readers probably know by now, the Codex Alimentarius Commission concerns itself with setting international food standards and guidelines. One of its committees, the Codex Committee on Food Labelling, is responsible for the labeling of organic foods. So, at its most recent meeting, its 42nd, in Rome, Italy, the week of October 20, 2014, the committee continued its review of the definitional standards for organic aquaculture (seafood).

The Canadian chairman, Paul Mayers, opened the meeting and quickly dispensed with some relatively minor, noncontentious agenda items.



However, when it came to the agenda item on revising the *Guidelines for the Production, Processing, Labelling and Marketing of Organic Foods*, the discussion quickly bogged down and became contentious.

India was the first to speak up, with its Dr. Gouri arguing strongly for the deletion of the exculpatory language in the guidelines' foreword ("Organic agriculture practices cannot ensure that products are completely free of residues due to general environmental pollution."). The National Health Federation (NHF) was the only other delegation to argue in support of India's position; and the chairman, in the first in a long series of incorrect decisions, told India and NHF that they missed the point, that Codex is "adjusting to industry practices," and that the language will stay in. In fact, it was the chairman who had missed the point.

Other language to the effect that aquaculture "production practices should aim to keep the impact on the environment low and consideration should be given to monitoring to ensure that this aim is achieved" was also on the chopping block. Strong opposition by the European Union, Norway, and India, however, did not stop the chairman from once again deleting protective wording from the organic guidelines.

Aquaculture production practices aimed at minimizing fertilizer dispersal from closed, farmed fish, and shellfish operations into open waters were next debated, with the European Union, Italy, and the National Health Federation arguing for retaining wording that such dispersal must be restricted. In this instance, even though the chairman argued for its dilution, he found a lack of consensus amongst the delegates and therefore the protective language was retained for debate at the next committee meeting.

With discussion then turning to the production methods for husbandry and breeding, the US adamantly stated its position, "We strongly support organic feed for organic animals." Argentina supported the US by also arguing that "natural feeds" should not be allowed as feed for organic animals

since the wording was too vague. The NHF stated its support for the Argentinean and American position, arguing further that the term *natural* is not sufficiently clear, would allow watered-down organic standards, and that in any event, by law, in the US at least, natural does not equate with organic. The Canadians, on the other hand, were all for wording that "where organic feed is not available, then natural feed could be used." Despite the strong opposition, the chairman of course went with the Canadian position and once again organic standards were further weakened.

The debate went on with Australia arguing that hormonal treatment should be allowed in certain instances ("brooding stock") for "organic" animals. Both South Africa and the NHF promptly spoke up to oppose hormonal use in organic animals, later supported by the Argentine delegate, who proposed that the wording say instead that "Hormonal treatment must not be used for production or growth." The chairman accepted this wording even though I argued once again that by limiting the prohibition to "production or growth," Codex would be implicitly allowing its use in all other circumstances, which was exactly what Australia wanted. The chairman replied that this could still be discussed at the next session, to which I replied that it would not be unless brackets were put around the language to signal to the delegates that the limitation on the hormone-use prohibition was still up for review. The brackets were left off. Thank you, Mr. Chairman.

The meeting marched on in the general direction of its murky definition and concept of organic. Mr. Mayers, serving as chairman of the committee for the last time and under the umbrella of the excuse that all of this wording was in an early stage of discussion, seemed to stumble along from one bad decision to another, mostly finding that – as he so sadly put it – "Codex is adjusting to industry practices." When the dust finally settled and the meeting thudded to an end, the committee had failed to consider three entire agenda items!

## Word Games

Whether at Codex or in one's own country, the food regulators and marketers know how to play word games. Keep calling the product "organic" but redefine it into something nonorganic. Still allow mistreatment of animals, overcrowding, pollution of them and the environment with poisons and toxins, and the use of nonorganic and synthetic feeds because consumers will naturally be fooled by the "organic" label into thinking that their foods and drinks are safer than and superior to the nonorganic slop palmed off on the masses.

What happened in Rome was a continuation of the horror that has pervaded our existence for far too long, where word meanings are twisted into their opposites, where they lose their plain meanings and people can no longer trust even the most basic words to mean what we think they say. If the Rome Codex meeting is any indication, the definition of *organic* will continue to be eroded worldwide, and it will not be a holiday to get its plain meaning back.

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This article has previously appeared in the *Health Freedom News* and *Whole Foods* magazines.

## Notes

1. CFR Regulatory Text, 7 CFR Part 205, Subpart A – Definitions. § 205.2 (terms defined); see <http://www.ams.usda.gov/nop/NOP/standards/DefineReg.html>. The full regulatory text may be found at Electronic Code of Federal Regulations (e-CFR): [http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&sid=3f34f4c22f9aa8e6d9864acc2683cea02&tpl=/ecfrbrowse/Title07/7cfr205\\_main\\_02.tpl](http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&sid=3f34f4c22f9aa8e6d9864acc2683cea02&tpl=/ecfrbrowse/Title07/7cfr205_main_02.tpl).
2. USDA National Organic Program. Organic food standards and labels. the facts [online brochure]. <http://www.ams.usda.gov/nop/Consumers/brochure.html>.
3. Council Regulation (EC) No. 834/2007 sets out the principles, aims, and overarching rules of organic production and defines how organic products are to be labeled. See *Official J Eur Union*. Feb. 2, 2007. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:189:0001:0023:EN:PDF> (especially Article 2, Definitions).
4. See USDA information at <http://www.ams.usda.gov/AMSV1.0/getfile?DocName=STELDEV3004446&acct=nopgeninfo>.

Scott C. Tips, JD, is a California-licensed attorney, legal columnist, and president and general counsel for the National Health Federation ([www.thenhf.com](http://www.thenhf.com)). He specializes in food-and-drug law and trademark law, but also engages in business litigation, general business law, and nonprofit organizations, with an international clientele.

# UWS and the Institute for Functional Medicine Sign Global Agreement

Since its inception, the Master of Science In Human Nutrition and Functional Medicine (HNFM) program at University of Western States (UWS) has incorporated innovative content from the Institute for Functional Medicine (IFM). Recently, the two institutions forged a stronger alliance and signed a global agreement that will lead to further collaboration between the two institutions, including integration of IFM's novel patient assessment criteria into the UWS program and IFM training for HNFM faculty. As part of the agreement, UWS and IFM have issued the following collaborative joint statement.

University of Western States (UWS) and the Institute for Functional Medicine (IFM) are pleased to announce a joint collaboration to incorporate functional medicine and functional nutrition coursework in the Master of Science in human nutrition and functional medicine (MSHNFM) program at UWS. UWS is an innovative university with a mission to improve the health of society and advance the science and art of integrated

health care. This collaboration will enable UWS to better prepare health professionals to address the 21st century epidemic of chronic diseases. IFM, the global leader in functional medicine education, is pleased to provide faculty training, faculty scholarships, and curricular materials and tools to support this innovative master's program. The MSHNFM program has been met with enthusiasm and interest among students from around the world and from a variety of backgrounds, including dietitians, nurses, physicians and several other professions.

Daniel Redwood, DC, director of the HNFM program, welcomed the signing of the UWS-IFM agreement.

"In our efforts to create the strongest possible program for our HNFM master's degree students, we are committed to providing our students and faculty with expanded opportunities for professional growth. This new agreement with IFM will help us to achieve both of these important goals," Redwood said.

He added, "Both IFM and UWS are institutions that increasingly

embody what so many of us have hoped for and spoken about for many years – interprofessional relationships that include not only mutual respect but active collaboration. We aspire to practice what we preach, enhance the quality of what we offer, and enlarge the range of ways we serve. Functional medicine principles and practices provide our students with a 21st century foundation."

## About University of Western States

University of Western States provides a science-driven curriculum that delivers a solid foundation and competitive edge in preparing students for clinical practice. UWS is a regionally accredited, nonprofit institution dedicated to improving the health of society through its educational programs, research, and clinical services. Founded in 1904, the university offers a doctor of chiropractic degree program; master's degrees in exercise and sports science, human nutrition and functional medicine, and diagnostic imaging; a massage therapy certification program; and approved continuing-education programs for licensed health-care professionals, and provides clinic services in five locations through Health Centers of UWS. UWS is a founding member of the Oregon Collaborative for Integrative Medicine, an organization that aims to advance integrative health care through education, research, patient care, and advocacy. To learn more about University of Western States and its academic programs, go to [www.uws.edu](http://www.uws.edu).

## OncANP 2015

by Jacob Schor, ND, FABNO

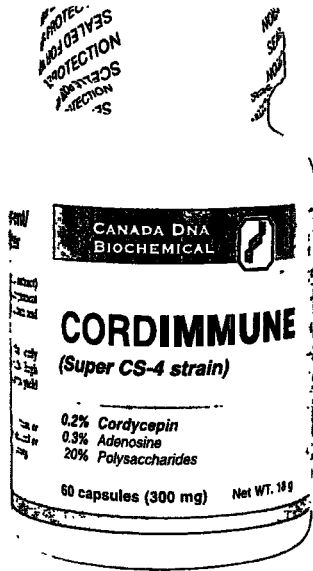
The Oncology Association of Naturopathic Physicians (OncANP) successfully held its fourth annual conference in Phoenix, Arizona, over this past Valentine's Day. The conference departed somewhat from the regular focus on only evidence-based integrative oncology and had several speakers who were patients rather than practitioners, patients who appear to have been successful in treating their own cancers with "mind-body based techniques." There were two other highlights for me: Dr. Davis Lamson was presented with an award for "lifetime achievement in the practice of naturopathic oncology." And, of course, Tina Kaczor and Lise Alschuler followed their now-established tradition of closing out these conferences with their rapid-fire summation of the most important research published in 2014 that has significant clinical implications in naturopathic oncology. Information on ordering conference recordings can be found at [www.oncanp.org](http://www.oncanp.org).



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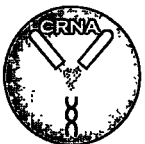


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# Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH  
www.INGRIDients.com

## A Classic Public Health Study Important for Today's Clinicians

### Introduction

A classic public health study emerged from a humanitarian crisis that ended 70 years ago this month. I present historical, scientific, and political perspectives based on my conversations with three men uniquely connected to the crisis. Their science and stories give today's clinicians a take-home message to glean, which I summarize at the end of this column.

### Overview

The Dutch Famine of 1944–1945 resulted when the Nazis blockaded Holland and flooded its fields in retaliation for its wartime resistance. Food was rationed to a few hundred calories a day from November through early May. Then Allied forces negotiated with the Nazis to allow food to be air-dropped to the Dutch people, effectively ending the famine in May 1945.

### Historical Perspective

The Center for Human Nutrition at Johns Hopkins University holds an annual lecture in memory of physician nutritionist and humanitarian Dr. George G. Graham. This year's lecture, "The Long Shadow of the Dutch Famine of 1944–1945," included Richard L. Hall, PhD, among its speakers.

Hall helmed the science and technologic advances of McCormick & Company during a period of expanding globalized trade. Less known is his first lifesaving nutrition intervention. Hall served as Navigator, 493rd Bomb Group, 8th Air Force, where he led the May 1945 food drop over Holland. Hall's inspiring collection of stories was instructive. It spoke to what lasts, what's remembered 70 years later.

**Kindness reciprocated.** Dr. Hall recounted a story of an international business meeting when the dinner conversation shifted to tulips as an export crop in Holland,

"When do the tulips bloom?" "May 6," answered Hall, causing surprise that an American took the question intended for the Dutch guests. Then he explained, "The Dutch wrote 'Thank You' for us in fresh-cut tulips as we flew above them."

**Make the best decision with what you've got.** Hall was certain that no nutritionist was consulted about what kind of food was dropped. Since food was being rationed in England at the time as well, the food included military rations. When someone in the audience wryly added, "Military rations included cigarettes at that time," Hall quickly put it in context. He reminded us that the Allied forces had to negotiate with the Nazis to even make the historic mission possible. If the Allied forces' bombers went slightly off course, the Nazis were to only shoot with red flares. Yet some planes took fire underscoring the safety concerns surrounding the humanitarian mission.

**Mindfulness.** "The British called the food drop Operation Manna, which was a good name for what we were doing, well, even if the food only came from a few hundred feet above." He then disparagingly shook his head at the American name for the mission, Operation Chowhound. He said that to this day he felt embarrassed by the insensitivity reflected in the name.

### Scientific Perspective

L. H. Lumey, MD, MPH, PhD, also spoke at the Johns Hopkins seminar. Scientists David Barker and Bertie Lumey together theorized that the Dutch children born in 1945 may be at increased risk of chronic diseases later in life because of the fetal exposure to famine. The lack of maternal food could alter how genes are turned on and off during development, a field of research now called epigenetics. Barker's hypothesis appeared in the 1992 *British Medical Journal* with the title "Fetal and Infant Origins of Adult Disease."

The birth cohort of the Dutch Famine had all the attributes an epidemiologist would want in a population cohort (a study design wherein a certain group of people who had an exposure of scientific interest are followed over time and compared to an unexposed control group). The Dutch kept meticulous birth records and military service records, and the government wanted to support the research. The population at that time was genetically similar. The famine had an abrupt onset and clear end, giving an "exposure window" seldom found in nutrition.

Overall the data substantiate Barker's hypothesis and fine-tune details relevant to public health. The researchers initially thought that the famine would increase the risk of cancer and cardiovascular disease in the birth cohort. Instead there was increased susceptibility to diabetes and schizophrenia. Molecular studies show that methylation pathways are disrupted and that diabetes occurs at a lower body weight. Another finding is that first trimester exposure caused greater effects long term, even though those exposed in the third trimester showed the early effects of low birth weight. The magnitude of the effects appear smaller than Barker would have projected. However, they seem distinct from genetic effects, such as mothers with greater body fat and therefore greater genetic risk of diabetes being more likely able to sustain a pregnancy during famine.

Research now in its third decade is involving the third generation, offspring of the original birth cohort. Ongoing studies include MRI analysis of body fat distribution, twin studies, comparison cohorts from famines worldwide, and maternal wartime stress exposure in the absence of famine.

### Political Perspective

An early collaborator of Barker's is Sir Peter Gluckman, MMedSC, DSc, the chief science advisor to the prime minister of New Zealand. He coauthored *The Fetal Matrix* (2005) and founded the Liggins Institute within the University of Auckland. The institute's research premise is that not only famine but inadequate nutrition of all forms can have lasting but preventable effects.

I had the opportunity to correspond with Gluckman about my NutriBee intervention and meet the lead

nutritionist at the Liggins Institute. I learned why my young son showed interest in my work when he told his schoolmates his mother works with a real knight. Perhaps in this political era of belt-tightening and corporate influence, public health does require brave defense in a shining armor sort of way.

### Summarizing the Relevance to Today's Clinical Practice

**Make the best decision with what you've got.** The shadow of the Dutch famine stretches 70 years and many questions continue. The food choices of our day are thought to adversely affect the fetal matrix in similar ways. Yet our public-health policies and health-care financing poorly reflect this knowledge. Some say that they are waiting for additional evidence, but they aren't disclosing that the population evidence which they want will realistically take 70 years from the time of exposure.

**Don't unnecessarily settle for determinism.** For my mother, who was malnourished during World War II, her epigenetically imposed health risk was identified early. She received great care and did all the right things, and now the only place her diagnosis is found is in old medical charts. I suspect that many Dutch citizens acted similarly, determined not to be shadowed by Nazi oppression. This type of human resilience may help explain why Lumey's January 2015 research findings published in the *American Journal of Epidemiology* show less effect in adult mortality from the Dutch famine birth cohort than might have been anticipated from earlier studies.

**Reframe the family dynamics.** In my experience, epigenetics helps some of my weight-management patients find the path to self-acceptance. The negative self-talk sounds like this, "My family is slim, but I'm not. I guess I just don't have willpower." Dedicated but discouraged, these dieters benefit from knowing that their dieting success may be harder to realize due to a well-accepted biologic reason.

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Editor, *Advancing Medicine with Food and Nutrients* (CRC Press; 2013)

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# Anti-Aging Medicine

by Ronald Klatz, MD, DO, and  
Robert Goldman, MD, PhD, DO, FAASP

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## An Anti-Aging Approach for Blood Pressure Management

Blood pressure is the force of blood pushing against the walls of your arteries. The US Centers for Disease Control (CDC) considers normal a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mmHg. Prehypertension is defined as a systolic reading between 120 and 139 mmHg and diastolic between 80 and 89 mmHg. Hypertension is a systolic pressure of 140 mmHg or higher and diastolic of 90 mmHg or higher.

Hypertension (high blood pressure) is called the “silent killer” because it often has no warning signs or symptoms. In fact, fewer than half (47%) of Americans with high blood pressure have the condition under control.

In the majority of cases, hypertension is readily modifiable. In this article, we review recent studies that suggest simple, effective, and natural approaches to prevent and/or control hypertension – a major risk factor for heart disease and stroke, two of the leading causes of death.

High blood pressure [Web page]. US Centers for Disease Control & Prevention. <http://www.cdc.gov/bloodpressure>. Accessed 27 Jan. 2015

Measuring blood pressure [Web page]. US Centers for Disease Control & Prevention. <http://www.cdc.gov/bloodpressure/measure.htm>. Accessed 27 Jan. 2015.

### Garlic Assists Blood Pressure Management

Daily dietary supplementation of garlic (*Allium sativum*) helps to reduce both systolic and diastolic blood pressures. Xiang-Jun Yang and colleagues from the First Affiliated Hospital of Soochow University (China) completed a meta-analysis of 17 randomized controlled trials that studied the effects of garlic powder, aged garlic extract, and garlic oil on blood pressure. The investigators revealed that the garlic supplements studied, ranging in dosages of 300 to 900 mg/day, reduced systolic blood pressure by 3.75 mmHg and diastolic blood pressure by 3.39 mmHg, among those people with hypertension (elevated blood pressure). The study authors submit: “This meta-analysis suggests that garlic supplements are superior to controls (placebo in most trials) in reducing [blood pressure], especially in hypertensive patients.”

Wang H-P, Yang J, Qin L-Q, Yang X-J. Effect of garlic on blood pressure: a meta-analysis. *J Clin Hypertens*. 5 Jan. 2015.

### Protein May Moderate Blood Pressure

Diets rich in protein foods may help to lower elevated blood pressure. Lynn Moore and colleagues from Boston University School of Medicine (Massachusetts, US) report

that a diet rich in protein foods may help to lower elevated blood pressure. The researchers analyzed protein intakes of healthy participants from the Framingham Offspring Study and followed them for development of high blood pressure over an 11-year period. Data revealed that those adults who consumed more protein, whether from animal or plant sources, had statistically significantly lower systolic blood pressure and diastolic blood pressure levels after 4 years of follow-up. In general, these beneficial effects were evident for both overweight (at/over 25 kg/m<sup>2</sup> BMI) and normal weight (at/less than 25 kg/m<sup>2</sup> BMI) individuals. The investigators also found that consuming more dietary protein also was associated with lower long-term risks for high blood pressure. When the diet also was characterized by higher intakes of fiber, higher protein intakes led to 40% to 60% reduction in risk. Observing, “Higher protein intakes were associated with lower mean [systolic blood pressure] and [diastolic blood pressure],” the study authors conclude: “Adults consuming more dietary protein from either plant or animal sources had lower long-term risks of [high blood pressure].”

Buendia JR, Bradley ML, Singer MR, Moore LL. Diets higher in protein predict lower high blood pressure risk in Framingham Offspring Study adults. *Am J Hypertens*. 2014 Sep 6; pii:hpu157.

### Bacteria Beat Blood Pressure

Abundantly found in yogurt, probiotics may help lower both systolic and diastolic blood pressures. Jing Sun and colleagues from Griffith University (Australia) analyzed data resulting from 9 clinical studies involving a total of 543 adults with normal and elevated blood pressure. Results revealed that probiotic consumption lowered systolic blood pressure by an average 3.56 mmHg, and diastolic blood pressure by an average 2.38 mmHg, as compared with adults who didn’t consume probiotics. The effects were evident after 8 weeks of probiotic consumption, with the researchers noting that probiotics containing a daily bacteria volume of between 10 billion and 1 trillion colony-forming units (CFU) were most effective in addressing blood pressure. The study authors write: “The present meta-analysis suggests that consuming probiotics may improve [blood pressure] by a modest degree, with a potentially greater effect when baseline [blood pressure] is elevated.”

Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. *Hypertension*. July 21, 2014.

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### Green Tea Supports Blood Vessels

Abundant in the antioxidant compounds epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC), green tea (*Camellia sinensis*) intake helps to manage blood pressure. I. Onakpoya and colleagues from the University of Oxford (UK) completed a meta-analysis of published randomized controlled trials involving 1536 participants, on green tea and its polyphenol constituents. They found that green tea consumption was associated with a lower average systolic blood pressure (1.94 mmHg). In addition, green tea consumption correlated to lower total and LDL cholesterol levels. The team speculates that mechanisms of action may include a relaxation of blood vessels, as well as lowering of prostaglandin E2. They also observe that green tea is abundant in antioxidants that have been shown to improve endothelial function. The study authors conclude: "Green tea intake results in significant reductions in systolic blood pressure, total cholesterol, and LDL cholesterol."

Onakpoya I, Spencer E, Heneghan C, Thompson M. The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis*. 31 January 2014.

### Mediterranean Soup Combats Hypertension

A cold vegetable soup known as gazpacho, featuring tomatoes, cucumbers, garlic, and olive oil, is rich in phytochemicals. A. Medina-Remon and colleagues from the University of Barcelona (Spain) analyzed data collected on 3995 Spanish participants in the PREDIMED trial, which aims to analyze the effects of Mediterranean diet on the population at risk for cardiovascular diseases. The researchers found that consumption of gazpacho was inversely associated with the incidence of high blood pressure (hypertension), reporting that the risk could be reduced by as much as 27%. Observing, "Gazpacho consumption was inversely associated with systolic and diastolic [blood pressure] and prevalence of hypertension in a cross-sectional Mediterranean population at high cardiovascular risk," the study authors submit: "The association between gazpacho intake and reduction of [blood pressure] is probably due to synergy among several bioactive compounds present in the vegetable ingredients used to make the recipe."

Medina-Remon A, Vallverdu-Queralt A, Arranz S, et al. Gazpacho consumption is associated with lower blood pressure and reduced hypertension in a high cardiovascular risk cohort. Cross-sectional study of the PREDIMED trial. *Nutr Metab Cardiovasc Dis*. 10 November 2012.

### Meditation with Yoga Reduces Blood Pressure

Blood pressure is effectively lowered by mindfulness-based stress reduction, a technique combining meditation and yoga, in people with borderline high blood pressure. Joel W. Hughes and colleagues from Kent State University (Ohio, US) enrolled 56 women and men diagnosed with prehypertension – blood pressure that is higher than desirable, but not yet so high that antihypertensive drugs would be prescribed. One group of patients was assigned to a program of Mindfulness-Based Stress Reduction (MBSR), which incorporated meditation and yoga: 8 group sessions of 2½ hours per week. Led by an experienced instructor, the sessions included three main types of mindfulness skills: body scan exercises, sitting meditation, and yoga exercises. Patients were also encouraged to perform mindfulness exercises at home. The other "comparison" group received lifestyle advice plus a muscle-relaxation activity. Blood pressure measurements were compared between groups to determine whether the mindfulness-based intervention reduced blood pressure in this group of people at risk of cardiovascular problems. Patients in the mindfulness-based intervention group had significant reductions in clinic-based blood pressure measurements. Systolic blood pressure decreased by an average of nearly 5 mmHg, compared with less than 1 mm Hg in the control group. Diastolic blood pressure was also lower in the mindfulness-based intervention group: a reduction of nearly 2 mmHg, compared with an increase of 1 mmHg in the control group.

Hughes JW, Fresco DM, Myerscough R, van Dulmen MHM, Carlson LE, Josephson R. Randomized controlled trial of mindfulness-based stress reduction for prehypertension. *Psychosom Med*. October 2013; 75:721–728

### Fitness Regimen Helps to Lower Blood Pressure

The American Heart Association (AHA) issued a statement in support of aerobic exercise, resistance or strength training, and isometric hand grip exercises to lower high blood pressure (hypertension). Robert D. Brook, chair of the AHA's research



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Dr. Nicholas DiNubile, MD

## Anti-Aging Medicine

▶ panel and an associate professor of medicine at the University of Michigan (US), reports that exercise-based regimens, including aerobic, dynamic resistance, and isometric handgrip modalities, have "relatively stronger supporting evidence," leading the panel to write: "It is the consensus of the writing group that it is reasonable for all individuals with blood pressure levels >120/80 mm Hg to consider trials of alternative approaches as adjuvant methods to help lower blood pressure when clinically appropriate."

Brook RD, Appel LJ, Rubenfire M, et al.; on behalf of the American Heart Association Professional Education Committee of the Council on High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. *Hypertension*. 2013 Apr 2.

### High Blood Pressure Linked to Alzheimer's

High blood pressure (hypertension), one of the most common risk factors of stroke and an accelerator of multiple forms of heart disease, especially when paired with excess body weight, is a leading chronic health concern worldwide. Emerging evidence suggests that the disease also plays a role in Alzheimer's disease. Daniel A. Nation and colleagues from the VA San Diego Healthcare System (California, US) studied 177 men and women, aged 65 to 100 years, who did not show symptoms of Alzheimer's disease at the study's start.

Participants had their pulse pressure (a marker of the aging of the vascular system, a calculation of the systolic minus diastolic reading) taken and lumbar punctures taken to obtain spinal fluid. The researchers found that people who have higher pulse pressure are more likely to have the Alzheimer's biomarkers amyloid-beta, or plaques, and p-tau protein, or tangles, in their cerebral spinal fluid than those with lower pulse pressure. For every 10-point rise in pulse pressure, the average level of p-tau protein in the spinal fluid rose by 1.5 picograms per milliliter. The relationship was found in people aged 55 to 70, but not in people aged 70 to 100. Writing, "[Pulse pressure] elevation is associated with increased [cerebrospinal fluid] P-tau and decreased A[beta]1-42 in cognitively normal older adults," the study authors submit: "Pulsatile hemodynamics may be related to amyloidosis and tau-related neurodegeneration."

Nation DA, Edland SD, Bondi MW, et al. Pulse pressure is associated with Alzheimer biomarkers in cognitively normal older adults. *Neurology*. 2013 Nov 13.

To stay updated on the latest breakthroughs in natural approaches for effective blood pressure management, visit the World Health Network ([www.worldhealth.net](http://www.worldhealth.net)), the official educational website of the A4M and your one-stop resource for authoritative anti-aging information. Be sure to sign up for the free Longevity Magazine e-journal, the A4M's award-winning weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity. ♦

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**APRIL 23-26: 18TH CLINICAL APPLICATIONS FOR AGE MANAGEMENT MEDICINE** in Orlando, Florida. CONTACT: [www.agedmed.org](http://www.agedmed.org); [conference@agedmed.org](mailto:conference@agedmed.org)

**APRIL 23-26: AMERICAN ACADEMY OF MEDICAL ACUPUNCTURE 27TH ANNUAL SYMPOSIUM** in St. Louis, Missouri. CMEs. CONTACT: [www.medicalacupuncture.org/ForPhysicians/Symposium.aspx](http://www.medicalacupuncture.org/ForPhysicians/Symposium.aspx)

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**APRIL 25-26: PARTNERS IN NUTRITION @** University of Western States in Portland, Oregon. CEUs for NDs, DCs, Nutrition Therapists. CONTACT: [bioticsnw.com/content/partners-nutrition](http://bioticsnw.com/content/partners-nutrition)

**APRIL 25-MAY 2: PHYSICIANS' ASSOCIATION FOR ANTHROPOSOPIHIC MEDICINE INTERNATIONAL POST GRADUATE MEDICAL TRAINING** in Fair Oaks, California. CONTACT: [www.paam.net/training/event-detail/article/2015-ipmt-notice-52.html](http://www.paam.net/training/event-detail/article/2015-ipmt-notice-52.html)

**APRIL 26: ADVANCED APPLIED KINESIOLOGY- For Dysbiosis, Lyme, Foods, Metals** in San Francisco, California. Treating the chronic patient. CONTACT: 970-201-1457; [www.MichaelLebowitzDC.com/html/SF2015](http://www.MichaelLebowitzDC.com/html/SF2015)

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**APRIL 30-MAY 2: 13TH ANNUAL INTERNATIONAL IPT/IPTLD INTEGRATIVE ONCOLOGY** in Reno, Nevada. CONTACT: 954-540-1896; [bestanswerforcancer.org](http://bestanswerforcancer.org); Sharon@bestanswerforcancer.org

**APRIL 30-MAY 3: NATIONAL ASSOCIATION FOR NUTRITION PROFESSIONALS 10TH ANNUAL CONFERENCE & EXPO** in St. Paul, Minnesota. CEUs for NDs and nutritionists. CONTACT: [www.nanp.org/conference/](http://www.nanp.org/conference/)

**MAY 1-3: HORMONE REPLACEMENT THERAPY SEMINAR (Session 1)** with Dr. Neal Rouzier in Las Vegas, Nevada. Also, **JULY 31- AUGUST 2** in Charlotte, North Carolina. CONTACT: [www.ducerecorp.com/Seminars.aspx](http://www.ducerecorp.com/Seminars.aspx)

**MAY 1-3: 59TH ANNUAL NORTHWEST NATUROPATHIC PHYSICIANS CONVENTION - Wisdom of our Elders** in SeaTac, Washington. CONTACT: [www.nwnpc.com/](http://www.nwnpc.com/)

**MAY 1-3: 14TH INTERNATIONAL CONFERENCE ON CONSCIOUSNESS IN AYURVEDA & YOGA** in Edison, New Jersey. CONTACT: [aapna.org/conferences/may-1-3-2015-edison-nj-usa](http://aapna.org/conferences/may-1-3-2015-edison-nj-usa)

**MAY 2: ORGANIC ACIDS WORKSHOP: An Invaluable Tool for Discovering the Underlying Causes of Chronic Illness** with Kurt Woeller, DO in Washington D.C. CONTACT: [www.greatplainslaboratory.com/home/eng/OATworkshop.asp](http://www.greatplainslaboratory.com/home/eng/OATworkshop.asp)

**MAY 2-6: MINDFUL PRACTICE ADVANCED WORKSHOP : ENHANCING QUALITY OF CARE, QUALITY OF CARING, AND RESILIENCE** in Batavia, New York. For healthcare practitioners. Also, **OCTOBER 14-17**. CONTACT: [www.urmc.rochester.edu/family-medicine/mindful-practice/presentations-workshops.aspx](http://www.urmc.rochester.edu/family-medicine/mindful-practice/presentations-workshops.aspx)

**MAY 4-6: 12TH ANNUAL NUTRITION & HEALTH CONFERENCE @ Arizona Center for Integrative Medicine** in Phoenix, Arizona. CONTACT: [nutritionandhealthconf.org/](http://nutritionandhealthconf.org/)

**MAY 6-9: 23RD ANNUAL WORLD CONGRESS ON ANTI-AGING MEDICINE** in Hollywood, Florida. CONTACT: 888-997-0112; [www.a4m.com/anti-aging-conference-2015-hollywood.html](http://www.a4m.com/anti-aging-conference-2015-hollywood.html)

**MAY 8-10: ICMART XVII WORLD CONGRESS ON MEDICAL ACUPUNCTURE** in Bali, Indonesia. CONTACT: [icmart.org/events/upcoming-icmart-congress/upcoming-icmart-congress.html](http://icmart.org/events/upcoming-icmart-congress/upcoming-icmart-congress.html)

**MAY 8-10: 10th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE** in Philadelphia, Pennsylvania. CONTACT: [www.homeopathycenter.org/2015-joint-american-homeopathic-conference/](http://www.homeopathycenter.org/2015-joint-american-homeopathic-conference/)

**MAY 10-14: GERSON THERAPY PRACTITIONER TRAINING-MODULE 1 (of 2)** in San Diego, California. In-depth training in Dr. Max Gerson's dietary healing principles. CONTACT: 800-838-2256; [aonken@gerson.org](mailto:aonken@gerson.org); [gerson.org/gerpress/practitioner-training/](http://gerson.org/gerpress/practitioner-training/)

**MAY 16: PATH FOUNDATION presents THE SECRET WEAPON & THE WAR ON DRUGS: BRAIN RESEARCH** in New York City, New York. CONTACT: 646-367-7411; [www.pathfoundationny.org](http://www.pathfoundationny.org)

**MAY 28-30: INSTITUTE FOR FUNCTIONAL MEDICINE 2015 ANNUAL INTERNATIONAL CONFERENCE** in Austin, Texas. CONTACT: <https://www.functionalmedicine.org/conference.aspx?id=2858&cid=0&section=t433>

**MAY 29-JUNE 1: MEDICINES FROM THE EARTH HERB SYMPOSIUM** in Black Mountain, North Carolina. CE credits available. CONTACT: 541-482-3016; [www.botanicalmedicine.org](http://www.botanicalmedicine.org)

**MAY 30-31: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION 2015 SPRING CONTINUING MEDICAL EDUCATION CONFERENCE** in Scottsdale, Arizona. CONTACT: [www.aznma.org/2015/02/aznma-spring-2015-conference/](http://www.aznma.org/2015/02/aznma-spring-2015-conference/)

**MAY 31- SEPTEMBER 12: COMPREHENSIVE TRAINING COURSE ON HERBAL MEDICINE FOR PHYSICIANS (Stage A & B) PREPARATORY PROGRAM & PRACTICAL SESSIONS** in San Francisco, California. AMA PRA Category 1 credits. CONTACT: 415-731-1330 or 888-882-1330 (toll free); [www.acupuncturecourse.org](http://www.acupuncturecourse.org)

**JUNE 5-7: NEURAL PROLOTHERAPY WORKSHOP** in Seattle, Washington. CONTACT: Jeff Harris, ND, 206-517-4748; [www.jeffharrisnd.com](http://www.jeffharrisnd.com)

**JUNE 5-7: HOMEOPATHY RESEARCH INSTITUTE 2015 CONFERENCE - Cutting Edge Research in Homeopathy** in Rome, Italy. CONTACT: [www.HRIRome2015.org](http://www.HRIRome2015.org)

**JUNE 6-7: SIBO SYMPOSIUM 2015 @ National College of Natural Medicine** in Portland, Oregon. Small intestine bacterial overgrowth. CONTACT: [sibosymposium.com/](http://sibosymposium.com/)

**JUNE 11-14: FOOD AS MEDICINE-CENTER FOR MIND/BODY MEDICINE** in Minneapolis, Minnesota. Also, **SEPTEMBER 18-22** in Stockbridge, Massachusetts. CONTACT: [cmbm.org/professional-trainings/food-as-medicine/](http://cmbm.org/professional-trainings/food-as-medicine/)

**JUNE 11 -14: MEMBRANE MEDICINE INTERNATIONAL SYMPOSIUM** in Las Vegas, Nevada. Addressing epigenetics, the microbiome and the brain with lipid therapy. Intensive Clinical PK Biomedical Course. CONTACT: NeuroLipid Research Foundation, 856-825-8338; fax 856-825-2143; [www.neurolipid.org/our-focus/membrane-medicine-biomedical-conference-series/](http://www.neurolipid.org/our-focus/membrane-medicine-biomedical-conference-series/)

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**JUNE 12-14: 12TH INTERNATIONAL HERB SYMPOSIUM** in Norton, Massachusetts. CONTACT: [www.internationalherbsymposium.com/index.php?route=common/home](http://www.internationalherbsymposium.com/index.php?route=common/home)

**JUNE 25-26: SopMED (Society of Oxidative and Photonic Medicine) INAUGURAL TRAINING AND CONFERENCE** in Salt Lake City, Utah. Ozone/UBI training and business workshops. Limited enrollment. CONTACT: 517-242-5813; [www.sopmed.org](http://www.sopmed.org); [info@sopmed.org](mailto:info@sopmed.org)

**JUNE 25-28: HEALTH FUSION- CANADIAN ASSOCIATION OF NATUROPATHIC DOCTORS NATIONAL CONFERENCE** in Calgary, Alberta, Canada. CONTACT: [https://www.cand.ca/Conference\\_Health\\_Fusion.healthfusion.0.html](https://www.cand.ca/Conference_Health_Fusion.healthfusion.0.html)

**JULY 4-5: WORLD CONGRESS ON NATURAL MEDICINE** in Havana, Cuba. Sponsored by The Sacred Medical Order. CONTACT: [www.smoch.org/world\\_congress\\_havana.php](http://www.smoch.org/world_congress_havana.php); [panamint@sisterisles.kn](mailto:panamint@sisterisles.kn)

**JULY 4-5: 5TH INTERNATIONAL NUTRITIONAL & ENVIRONMENTAL CONFERENCE** in Cochin, India. CONTACT: [www.inma.co.in/](http://www.inma.co.in/)

**JULY 17-19: 21ST ANNUAL INTERNATIONAL INTEGRATIVE MEDICINE CONFERENCE** in Melbourne, Australia. CONTACT: <https://www.aima.net.au/21st-annual-international-integrative-medicine-conference/>

**AUGUST 5-8: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS (AANP) 30TH ANNIVERSARY CONFERENCE** in Oakland, California. CONTACT: [www.naturopathic.org/aanp2015](http://www.naturopathic.org/aanp2015)

**AUGUST 19-22: 24TH ANNUAL IAACN SCIENTIFIC SYMPOSIUM – PREVENTIVE BIOCHEMICAL INTERVENTIONS & NOVEL THERAPEUTIC OVERTURES FOR THOSE WITH CANCER™** in Minneapolis, Minnesota. CONTACT: [www.iaacn.org/symposium/](http://www.iaacn.org/symposium/)

**AUGUST 21-23: INTEGRATIVE ADDICTION 2015** in Myrtle Beach, South Carolina. CONTACT: 954-540-1896; [Sharon@integrativeaddiction2015.com](mailto:Sharon@integrativeaddiction2015.com); [integrativeaddiction2015.com](http://integrativeaddiction2015.com)

**SEPTEMBER 11-13: CURING THE INCURABLES** in St. Louis, Missouri. Fibromyalgia and chronic fatigue. CONTACT: [iamconf.com](http://iamconf.com)

**SEPTEMBER 14-15: 15th INTERNATIONAL CONFERENCE ON AYURVEDIC MEDICINE** in Paris, France. CONTACT: [aapna.org/conferences/15th-conference-september-2015-paris-france](http://aapna.org/conferences/15th-conference-september-2015-paris-france)

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**SEPTEMBER 25-27: 3RD ANNUAL LIFESTYLE MEDICINE SUMMIT** in Phoenix, Arizona. CONTACT: [https://www.metagenics.com/events/2015\\_lifestyle\\_medicine\\_summit](https://www.metagenics.com/events/2015_lifestyle_medicine_summit)

**SEPTEMBER 25-27: WORLD FEDERATION OF ACUPUNCTURE-MOXIBUSTION SOCIETIES INTERNATIONAL CONFERENCE** in Toronto, Ontario, Canada. CONTACT: [wfastoronto2015.com/](http://wfastoronto2015.com/)

**OCTOBER 1-4: 13TH ANNUAL RESTORATIVE MEDICINE CONFERENCE** in Blaine, Washington. CONTACT: [restorativemedicine.org/conference/2015/](http://restorativemedicine.org/conference/2015/)

**OCTOBER 2-4: HORMONE REPLACEMENT THERAPY SEMINAR (Session 2)** with Dr. Neal Rouzier in Chicago, Illinois. CONTACT: [www.ducerecorp.com/Seminars.aspx](http://www.ducerecorp.com/Seminars.aspx)

**OCTOBER 9-11: 17th INTERNATIONAL CONFERENCE ON AYURVEDA & AUTOIMMUNE DISORDERS** in San Jose, California. CONTACT: [aapna.org/conferences/17th-conference-october-9-11-2015-san-jose-ca-usa/](http://aapna.org/conferences/17th-conference-october-9-11-2015-san-jose-ca-usa/)

**OCTOBER 24-29: 16TH ANNUAL SCIENCE AND CLINICAL APPLICATION OF INTEGRATIVE HOLISTIC MEDICINE** in San Diego, California. CONTACT: [www.scripps.org/events/people-planet-purpose-global-practitioners-united-in-health-healing-october-25-2015](http://www.scripps.org/events/people-planet-purpose-global-practitioners-united-in-health-healing-october-25-2015)

**OCTOBER 27 - NOVEMBER 2: 42nd BIOLOGICAL MEDICINE TOUR TO GERMANY & BADEN-BADEN MEDICINE WEEK - "Clinical Applications in Biological Medicine."** Includes "Medicine Week" Congress, exclusive OIRF English language lectures, and instrumentation, clinic and pharmacy presentations. CONTACT: Occidental Institute at 800-663-8342 or 250-490-3318; fax 250-490-3348; [support@oirf.com](mailto:support@oirf.com); [www.oirf.com](http://www.oirf.com)

**OCTOBER 28-NOVEMBER 1: ICIM CONFERENCE – ENERGY & MEDICINE: PARADOX & CONTROVERSY** in Chicago, Illinois. CONTACT: [www.IntegrativeMedicineConference.com](http://www.IntegrativeMedicineConference.com)

**NOVEMBER 7-8: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION 2015 FALL CONTINUING MEDICAL EDUCATION CONFERENCE** in Scottsdale, Arizona. CONTACT: [www.aznma.org](http://www.aznma.org)

**NOVEMBER 11-14: 56TH AMERICAN COLLEGE OF NUTRITION ANNUAL CONFERENCE** in Orlando, Florida. CONTACT: [www.naturalhealthresearch.org/annual-conference/](http://www.naturalhealthresearch.org/annual-conference/)

**NOVEMBER 12-14: SOCIETY FOR ACUPUNCTURE RESEARCH 2015 CONFERENCE** in Boston, Massachusetts. CONTACT: [www.acupunctureresearch.org/events](http://www.acupunctureresearch.org/events)

**NOVEMBER 12-15: AMERICAN FUNCTIONAL MEDICINE ASSOCIATION ANNUAL CONFERENCE** in Atlanta, Georgia. CONTACT: 1-855-500-2362; [www.afmassociation.com/calendar/](http://www.afmassociation.com/calendar/)

**NOVEMBER 13-15: IGNITE CONFERENCE 2015 – The Business of Better Medicine** in San Diego, California. CONTACT: [eeignite.com/coming-soon-the-business-of-better-medicine](http://eeignite.com/coming-soon-the-business-of-better-medicine)

**NOVEMBER 14-16: 12TH INTERNATIONAL CONFERENCE OF THE SOCIETY FOR INTEGRATIVE ONCOLOGY** in Boston, Massachusetts. CONTACT: [www.integrativeonc.org/index.php/sio-international-conferences](http://www.integrativeonc.org/index.php/sio-international-conferences)



# Women's Health Update

by Tori Hudson, ND  
womanstime@aol.com

## Hormone Therapy and Blueberries and Cardiovascular Disease in Postmenopausal Women

### Hormone Therapy and Timing of Hormone Therapy Providing Cardiovascular Protection

The long saga of menopausal hormone therapy and whether it decreases or increases the risk of cardiovascular disease has been increasingly focused on the timing hypothesis in the last 12 years since the publication of the initial Women's Health Initiative (WHI) randomized clinical trial results in 2002. Prior to that publication, many if not most conventional prescribers of hormone therapy (HT) specifically prescribed HT to prevent coronary artery disease (CAD) due to evidence that there was decreased mortality from 30% to 50%. However, the results of the WHI reported an increased incidence of cardiovascular disease in women on HT. Since that time, there has been the evolution of the "timing hypothesis." The cumulative observational evidence in the literature is consistently compelling that if HT is started within 10 years of menopause, there is indeed a reduced risk of cardiovascular disease, but after 10 years, there is an increased risk, which would be consistent with the older women studied in the original WHI trial.

In the current Finnish national analysis, all HT users since 1994 were included in a national health insurance database, which allows a good study of HT use and CAD. The researchers assessed the use of systemic HT and CAD mortality from 1995 to 2001, before the WHI and from 2002 to 2009, after the WHI. In Finland, as in many countries, the use of HT dropped significantly in 2002 due to the WHI publication. In the current report, more than 29,000 HT users were compared and age matched and postmenopause matched with the background population. During the pre-WHI time period, HT use was associated with a reduced CAD mortality of 29% for those who used HT for 1 or less years and 43% for 1 to 8 years of use. After the 2002 WHI, the reductions were 18% and 54% respectively and were similar if estrogen/progestin or estrogen only. The CAD mortality protection related to HT was greater in users young than 60 (i.e., <10 years postmenopause).

**Comment:** These Finnish findings that protection in CAD mortality was greater in younger menopausal women is consistent with numerous other studies which support this

"timing hypothesis" (e.g., the EPAT trial, the WELL-HART trial) and that estrogen is beneficial to healthy coronary vessels in younger women but not in older women for whom CAD is higher. The completion and results of the Early versus Late Intervention Trial (ELITE), the only clinical trial designed to specifically test the timing hypothesis of HT in postmenopausal women, is eagerly awaited as a timely and important study related to atherosclerosis progression in coronary artery disease.

Tuomikoski P et al. Coronary heart disease mortality and hormone therapy before and after the Women's Health Initiative. *Obstet Gynecol* 2014 Nov;124:947.

### Blueberry Consumption Improves Blood Pressure in Postmenopausal Women

Hypertension is a known major risk factor for the development of cardiovascular disease (CVD), the leading cause of death in the US. While hypertension does increase with aging in both men and women, in postmenopausal women, the increased incidence of high blood pressure is greater than in men. Fortunately, hypertension is by and large a preventable disease.

This 8-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 48 postmenopausal women with prehypertension and stage 1 hypertension. Women were randomized to receive either 22 g of freeze-dried blueberry powder or 22 g of control powder. Participants consumed 11 g of mixed powder with 1 cup of water twice per day about 6 to 8 hours apart.

Resting arterial systolic and diastolic blood pressures were evaluated and arterial stiffness was assessed as



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## Women's Health Update

well. Tests including C-reactive protein, nitric oxide, and superoxide dismutase were measured at baseline, 4 weeks, and 8 weeks.

After the 8-week period, systolic blood pressure (138 at baseline and 131 after treatment) and diastolic blood pressure (80 at baseline and 75 after treatment) were significantly improved in the blueberry group with no changes in the group receiving the control. These effects can also be stated as a 5.1% decrease in systolic blood pressure and 6.3% reduction in diastolic blood pressure. There was a significant reduction in brachial-ankle pulse wave velocity (baPWV), in the blueberry group and no changes in the control group. There was no effect of blueberry on mean arterial pressure, carotid-femoral pulse wave velocity (cfPWV) and heart rate at any point. There were no significant changes in C-reactive protein in either group, and superoxide dismutase levels were significantly increased at 4 and 8 weeks compared with baseline in both blueberry and control groups. Nitric oxide levels were significantly increased only in the blueberry group at 8 weeks compared with baseline.

The authors concluded that daily use of 22 g per day of freeze-dried blueberry powder for 8 weeks in postmenopausal women with prehypertension and stage I hypertension improves the blood pressure and arterial stiffness, and does so through enhanced nitric oxide-mediated vasodilation.

**Comment:** Other research has shown that 50 g/day of blueberry powder resulted in a 6% and 4% reduction in systolic BP and diastolic BP respectively, in obese men and women with metabolic syndrome. Epidemiologic and clinical treatment studies have also demonstrated that flavonoids and flavonoid rich foods can improve arterial stiffness as measured by pulse wave velocity. In the current study, the composite measure of aortic and peripheral arterial stiffness (baPWV) was significantly reduced in the blueberry group after the 8 weeks, even though there was no change in the gold standard of aortic stiffness, the cfPWV measurement, in either group. These findings indicate

that dietary interventions, such as blueberry powder, may be more effective for the peripheral arteries than central arteries but it is the pulse wave velocity in the peripheral arteries that may be more predictive of the progression of prehypertension to hypertension. In addition, it has been baPWV that has been reported to be an independent predictor of coronary atherosclerosis in postmenopausal women.

One of the suggested mechanisms related to increased blood pressure and arterial stiffness is endothelial dysfunction. Other research has demonstrated that improvements in flow-mediated vasodilation, an indicator of enhanced endothelial function, were closely related to blueberry polyphenol metabolites, which enhanced nitric oxide bioavailability. This is consistent with the current study of blueberry consumption's increasing nitric oxide levels, likely by increasing nitric oxide production rather than bioavailability.

One thought that I'm left with is whether fresh blueberries would be as good, or even better. It has been reported that freeze-drying may reduce anthocyanin content; however, even so, it led to an increase in other polyphenols which also impart a vascular effect of improved vasodilation. I would suggest that regular consumption of blueberries over time could have a delaying effect on the progression of atherosclerosis and thus possibly reduce the cardiovascular risk in postmenopausal women. The freeze-dried blueberry powder or frozen blueberries will be the more likely item accessible year round.

Johnson S, Figueroa A, Navaei N, et al. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre and stage I-hypertension. A randomized, double-blind, placebo-controlled clinical trial / *J Acad Nutr Diet*. Epub Jan 21, 2015. pii:S2212-2672(14)01633-5. doi:10.1016/j.jand.2014.11.001.

Dr. Tori Hudson graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in many capacities over the last 28 years. She is currently a clinical professor at NCNM and Bastyr University; has been in practice for over 30 years; and is the medical director of the clinic A Woman's Time in Portland, Oregon, and director of research and development for Vitonica, a supplement company for women. She is also a nationally recognized author, speaker, educator, researcher, and clinician. ♦

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# Dr. Ohhira's Probiotics Tallying Up Awards with a Duo of Respected Industry Distinctions

Dr. Ohhira's Probiotics Original Formula has once again garnered industry accolades by winning two prestigious awards, bringing the total to 13 and counting for this revolutionary whole-food supplement!

"For the inaugural launch of the new award, *Gluten Free Retailer* (GFR) polled its readers on their top-selling gluten-free products to compile its 2014 'Best of Gluten Free Awards.' After all, who is better qualified to determine the industry's best-selling products than the people who sell them?" said Janet Poveromo, editor in chief of *Gluten Free Retailer*. Dr. Ohhira's Probiotics was honored in the Dec./Jan. 2014 issue with the distinction of being named the "Best Selling" Gluten Free Supplement.

*Clean Eating* magazine also chose Dr. Ohhira's Probiotics for the coveted "Clean Choice Award," announced in the March 2015 issue.

"With more and more companies working to create clean and healthy packaged products and supplements, we feel it's important to reward their innovation and service to healthy eaters living a clean lifestyle," said Alicia Rewega, editor in chief of *Clean Eating* magazine. "In every way, clean eating is all about consuming whole food and supplements in its most natural state, or as close to it as possible."

Rewega conveyed that choosing the "Clean Choice Award" winners was a six-pronged process that involved taste, mouth feel, addictiveness, *Clean Eating*-approved ingredients, responsible packaging, and timesaving convenience. Each staff-tested product was rated on a scale from 1 to 5 in each of the six categories, with the highest scores winning.

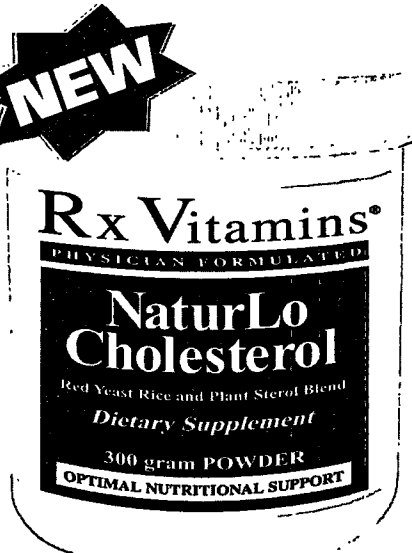
All of Dr. Ohhira's formulations are hand made in Japan with a true respect for nature and reverence for science. Dr. Ohhira's Probiotics is a whole-food supplement originating from all natural ingredients fermented for 3 to 5 years, which helps assure superior digestion. Containing live, viable

bacteria that encourage the growth of an individual's distinctive flora, this one-of-a-kind probiotic supports immune health while assisting with the digestion

of key micronutrients that encourage whole health for the entire family. For additional information, please visit [www.essentialformulas.com](http://www.essentialformulas.com).

PHYSICIAN FORMULATED

# NaturLo Cholesterol



## Red Yeast Rice and Plant Sterol Blend Dietary Supplement

**300 gram POWDER**

**One Scoop (one teaspoon) Provides:**


Phytosterol Complex (providing beta sitosterol, campesterol & stigmasterol)	1250 mg
Red Yeast Rice (citricin free) ( <i>monascus purpureus</i> )	1200 mg
Other Ingredients: Dark Chocolate flavoring, fruit sugar	

**Recommended Usage:**  
As a dietary supplement, take 1 level scoop (1 teaspoon) in the morning before breakfast and 1 level scoop in the evening before dinner. Recommended to be mixed in soy or skim milk.

**NaturLo Cholesterol** is designed to support the maintenance of HDL cholesterol and triglycerides within normal ranges. The formula helps maintain healthy cholesterol levels with natural and effective ingredients.\*

NaturLo Cholesterol is a powerful combination of red yeast rice and a plant sterol blend. It is a safe addition to any diet and exercise program.

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OPTIMAL NUTRITIONAL SUPPORT



## Vitamin B12: Which Routes of Administration and Which Forms Are Best?

Vitamin B12 is a group of cobalt-containing compounds that are collectively called cobalamins. The biologically active coenzyme forms of vitamin B12 that play a role in human metabolism are methylcobalamin and 5-deoxyadenosylcobalamin (commonly known as adenosylcobalamin). Vitamin B12 is involved in DNA synthesis, red blood cell formation, homocysteine metabolism, and synthesis of S-adenosylmethionine, and is essential for the normal functioning of the nervous system and immune system.

The main use for vitamin B12 is to prevent and treat vitamin B12 deficiency. However, this vitamin has also been used for a wide range of other conditions, including bursitis, hepatitis, idiopathic facial paralysis (Bell's palsy), vitiligo, herpes zoster, hyperhomocysteinemia, sciatica, trigeminal neuralgia, depression, dementia, chronic fatigue, neurodermatitis, diabetic neuropathy, hyperthyroidism, asthma, infertility, tobacco amblyopia, and cyanide poisoning.

### Routes of Administration

Vitamin B12 preparations are available for oral, sublingual, intranasal, and parenteral (intramuscular, subcutaneous, or intravenous) administration. Oral supplements are generally effective for preventing and treating vitamin B12 deficiency. Even patients with vitamin B12 malabsorption secondary to pernicious anemia can be effectively treated with oral supplements, provided that a sufficient dosage is used (500–1000  $\mu\text{g}$  per day) and the patient adheres to the recommended treatment regimen. However, since failure to correct vitamin B12 deficiency can lead to permanent neurological damage, periodic intramuscular injections may be preferable to oral supplementation when compliance with oral treatment is uncertain. Sublingual vitamin B12 does not appear to be absorbed more efficiently than oral vitamin B12.<sup>1</sup>

Vitamin B12 given intranasally produced higher peak plasma vitamin B12 concentrations than those achieved with oral administration, but lower concentrations than those obtained

with intramuscular injections.<sup>2</sup> However, the long-term safety of intranasal vitamin B12 has not been demonstrated, and it is possible that it could damage the nasal mucosa. Administration of vitamin B12 by inhalation resulted in a rapid increase in serum vitamin B12 levels, indicating that the vitamin was absorbed through pulmonary alveoli. However, pulmonary damage could result from this route of administration, since pulmonary fibrosis has occurred in dogs exposed to prolonged inhalation of cobalt.<sup>3</sup> Because of the lack of long-term safety data, I have avoided the use of intranasal and inhaled vitamin B12 preparations.

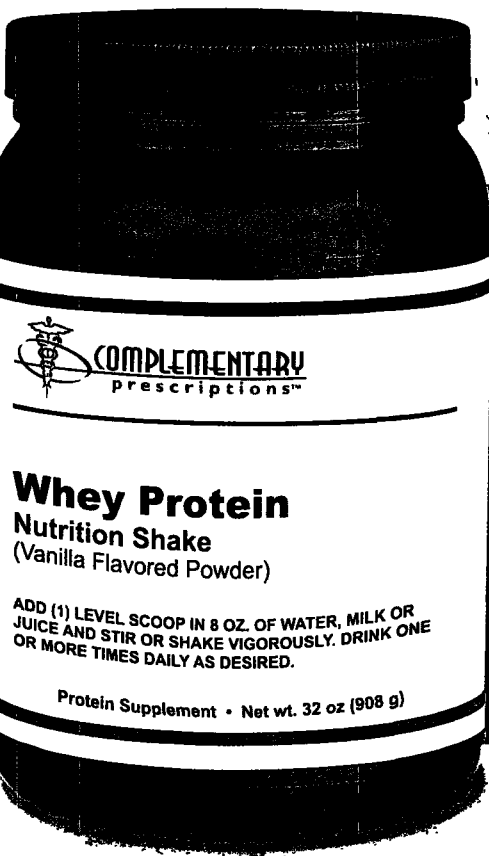
For most of the conditions that respond to vitamin B12, the vitamin probably does not work by correcting a deficiency. Rather, it may exert a pharmacological effect or compensate for impaired uptake of vitamin B12 into specific body tissues. In patients who are not vitamin B12 deficient, treatment efficacy usually seems to depend on the attainment of supraphysiological serum

*continued on page 104* ►



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► continued from page 102

concentrations, concentrations that can be achieved only by parenteral administration. For that reason, patients who improve with intramuscular injections often do not respond to oral, sublingual, or intranasal therapy. Subcutaneous injections have not been widely used in clinical trials, but they are said to cause less local burning than intramuscular injections.<sup>4</sup> Intravenous vitamin B12 may be less effective than intramuscular injections, presumably because the transiently high serum levels that follow intravenous administration may cause more of the vitamin to be lost in the urine.

## Forms of Vitamin B12

Cyanocobalamin is the most widely used form of vitamin B12, because of its stability and low cost, and because it can be converted in vivo to the biologically active forms of vitamin B12. However, only traces of cyanocobalamin occur naturally in the human body, which contains primarily hydroxocobalamin, adenosylcobalamin, and methylcobalamin. In addition, treatment with cyanocobalamin leads to the release of small amounts of cyanide, which may be atherogenic or otherwise harmful to patients who are unable to excrete cyanide efficiently because of impaired renal function. It has been suggested that the failure of some homocysteine-lowering studies to produce clinical benefit was due to the use of cyanocobalamin in patients with mild renal impairment.

Hydroxocobalamin does occur naturally in the human body. It is a stable form of vitamin

B12 that can be converted to the active coenzyme forms. Hydroxocobalamin does not contain a cyanide molecule, and is therefore safer than cyanocobalamin for patients who are sensitive to the deleterious effects of small doses of cyanide. In addition, unlike cyanocobalamin, hydroxocobalamin is a powerful cyanide antagonist, and therefore is of value in the treatment of tobacco amblyopia and cyanide poisoning. Furthermore, as compared with cyanocobalamin, hydroxocobalamin treatment produces higher and more sustained serum vitamin B12 levels.<sup>5,6</sup> For these reasons, hydroxocobalamin is highly preferable to cyanocobalamin, and some investigators have recommended that cyanocobalamin be withdrawn from the market.

Methylcobalamin, one of the coenzyme forms of vitamin B12, has been shown to be beneficial in the treatment of several medical conditions. In recent years, some investigators and supplement companies have argued that methylcobalamin is the preferred form of vitamin B12 for supplementation because it is biologically active. However, no comparison studies have been done, and there is no clear evidence that methylcobalamin is preferable to hydroxocobalamin. Likewise, there is no clear evidence that adenosylcobalamin (the other coenzyme form of vitamin B12) is preferable to hydroxocobalamin, except in the treatment of a rare inborn error of adenosylcobalamin biosynthesis.<sup>7</sup>

A potential disadvantage of methylcobalamin is that it

cannot apparently be converted to adenosylcobalamin.<sup>8</sup> Each of these coenzyme forms of vitamin B12 has distinct biochemical functions, and they serve as cofactors for different enzymes. Whereas treatment with hydroxocobalamin or cyanocobalamin would increase the concentration of both biologically active forms of vitamin B12, treatment with methylcobalamin may not increase the concentration of adenosylcobalamin. That fact may be particularly important when treating vitamin B12 deficiency.

Based on the limited evidence available, hydroxocobalamin appears to be the preferred form of vitamin B12 for therapeutic use. Additional research is needed to determine in what situations, if any, methylcobalamin has an advantage over hydroxocobalamin. If methylcobalamin is used to treat vitamin B12 deficiency, it may be prudent to administer it in combination with other forms of vitamin B12.

Alan R. Gaby, MD

## Notes

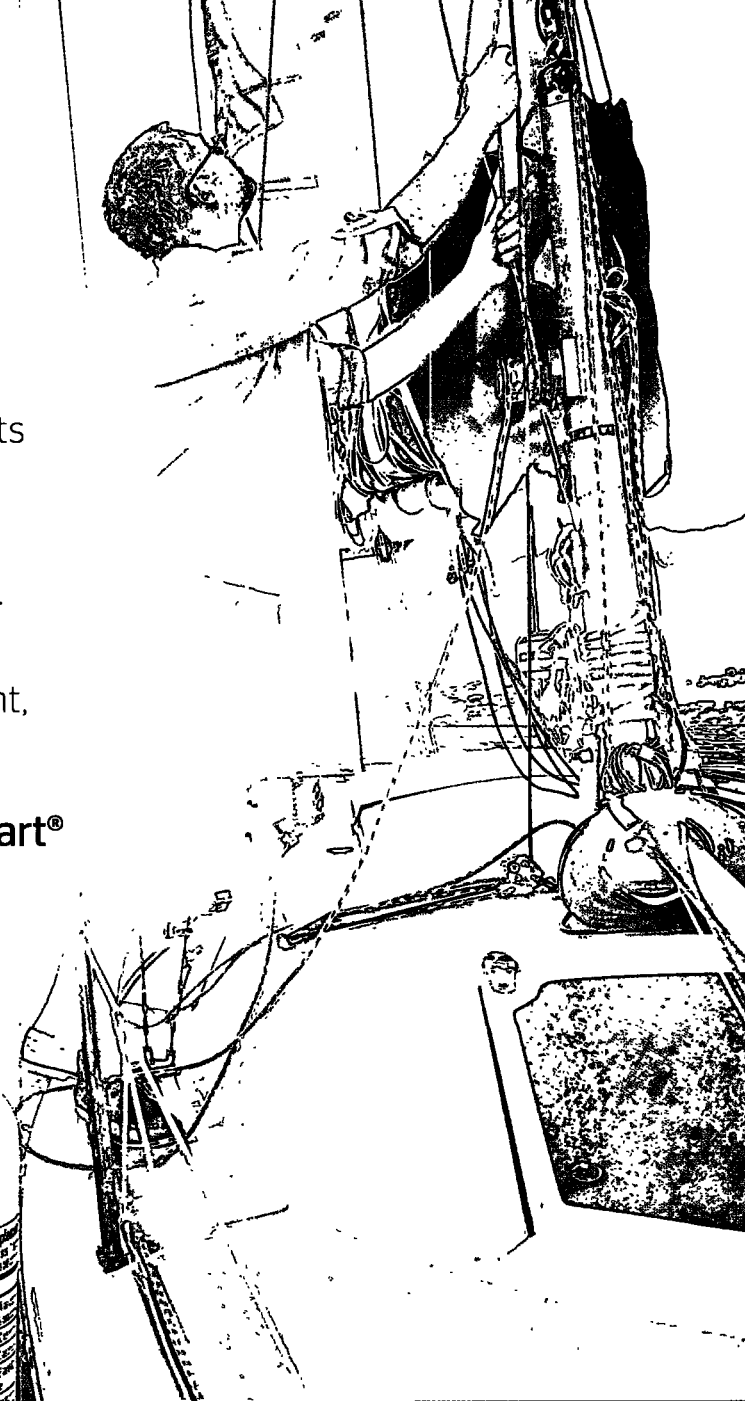
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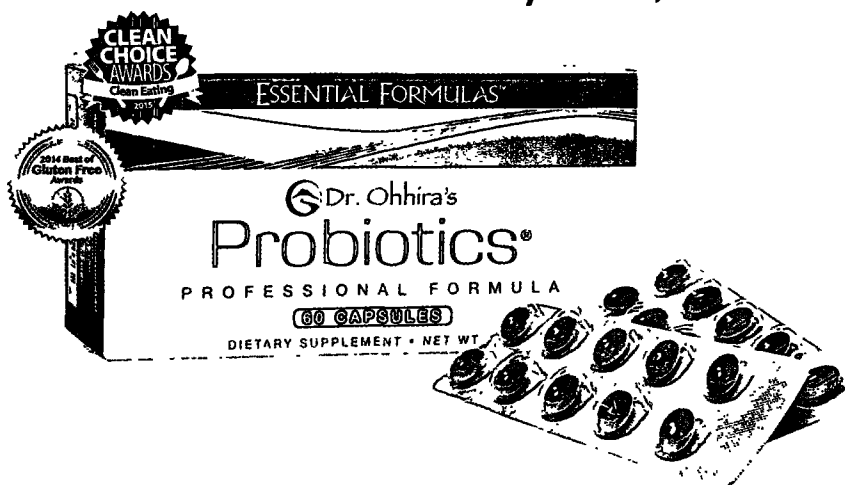


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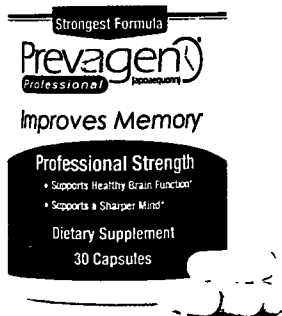
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Prevagen Professional is a safe and well-tolerated supplement for better memory.\* Prevagen has no known drug or supplement interactions. Prevagen is made without common allergens.

### Supplement Facts

Serving Size: 1 capsule		
Servings per container: 30		
Amount per capsule	% Daily Value	
Sodium	20 mg	<1%*
Apoaeguorin	40 mg	†
* Percent Daily Values are based on a 2,000 calorie diet		
† Daily Value not established		

**Other ingredients:** white rice flour, cellulose, salt, vegetable sourced magnesium stearate, acetic acid.

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Serving Size: 2 capsules  
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	Amount Per Serving	% Daily Value**
Vitamin B-6	10.0 mg	500%
Vitamin B-12 (as methylcobalamin)	2500.0 mcg	41,667%
NeuroTransmitter™ Complex	650.1 mg	
L-Glutamine (free form), L-tyrosine, Phosphatidyl Serine, Huperzine A		
Ultimate Focus™ Complex	780.0 mg	
Acetyl-L-carnitine, Vinpocetine		

\* Daily Value not established.

Other Ingredients: Vegetable cellulose (capsule shell), dicalcium phosphate, silica

CogniCare® provides a comprehensive cognitive support formula with proprietary blends of the most researched nutrients for mental clarity and processing activities.\*

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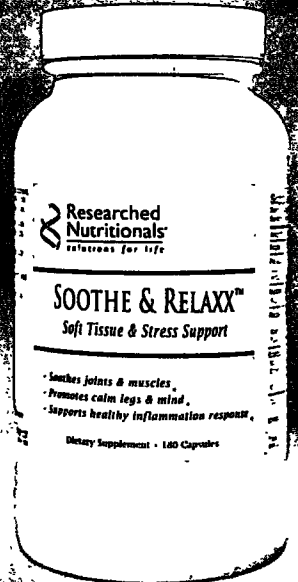
### Supplement Facts

Serving Size: 3 Capsules Servings per Container: 60

	Amount Per Serving	% Daily Value
Folic Acid (as 5-methyl-tetrahydrofolate)	800 mcg	200%
Pro Joint Soothers™	1375 mg	
Glucosamine Sulfate, MSM, Chondroitin Sulfate, Hyaluronic Acid		
Muscle & Leg Calmer™	750 mg	
Magnesium hydroxide, Malic acid		
Relaxx™ Complex	275 mg	
5-HTP (as 5-hydroxy tryptophan), Valerian, Lemon Balm, Passion Flower, German Chamomile		
ExInflame™ Complex	165 mg	
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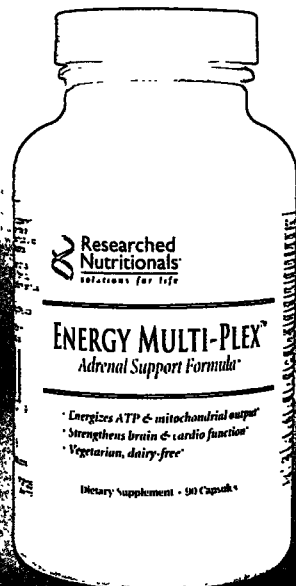
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Supplement Facts		
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	Amount Per Serving	% Daily Value
Pantothenic Acid (as d-calcium pantothenate)	25 mcg	250%
Vitamin B12 (as methylcobalamin)	500 mcg	8,333%
Magnesium (as magnesium aspartate)	24 mg	6%
Potassium (as potassium aspartate)	80 mg	2%
EnergyMax™ Complex	250 mg	•
D-Ribose, Panax Ginseng	350 mg	•
MuscularEnergy™ Complex	•	•
Malic Acid, Rhodiola Rosea	•	•
Mitochondria Energizer™ Complex	700 mg	•
Acetyl-L-Carnitine, Alpha Lipoic Acid	•	•
Metabolism Plus™ Complex	110 mg	•
Pyruvic Acid, 7-Keto DHEA	•	•
(3-Acetyl-7-oxo-dehydroepiandrosterone)	•	•
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Co-Enzyme Q-10, L-Taurine	•	•

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Other Ingredients: vegetable cellulose (capsule shell), cellulose, silica



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	Amount Per Serving	% Daily Value*
Calories	25	
Calories from Fat	0	
Total Carbohydrate	6g	2%
Sugars	5g	**
Magnesium Gluconate (elemental)	40 mg	10%
D-Ribose	5g	**
CardioPerform™	1g	**
Proprietary blend of L-carnitine (from lumarate) and Acetyl L-carnitine	•	•
Malic Acid	240 mg	**

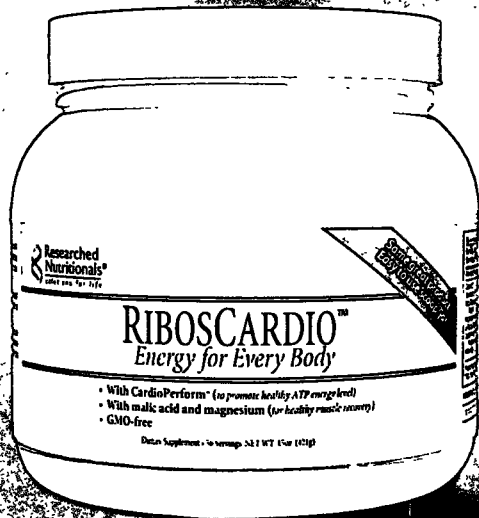
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