Cardiovascular Health | Seasonal Allergies

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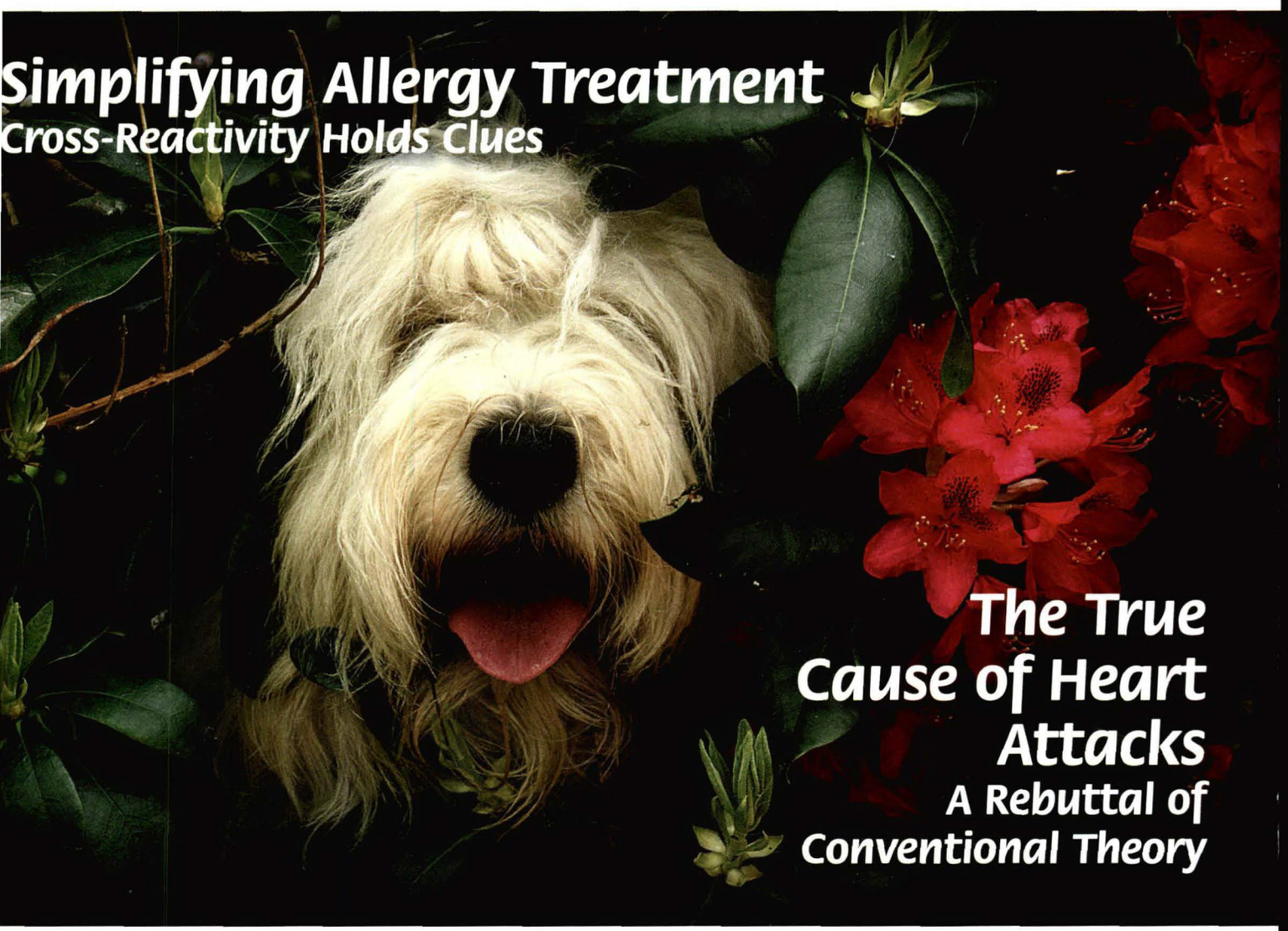
Townsend Letter

The Examiner of Alternative Medicine



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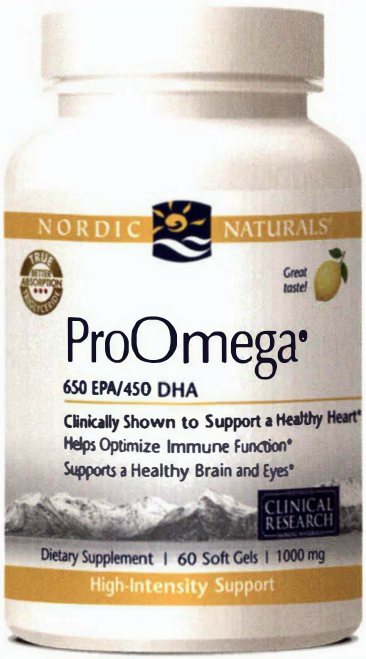

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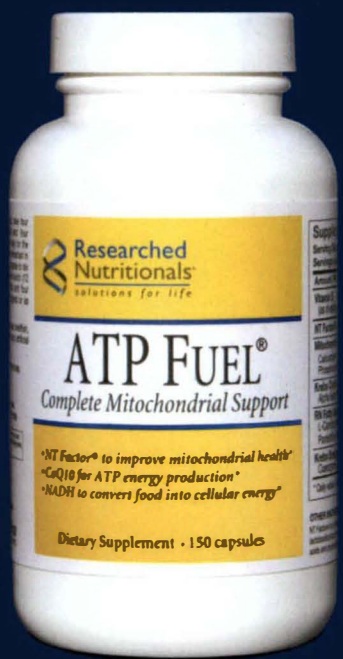

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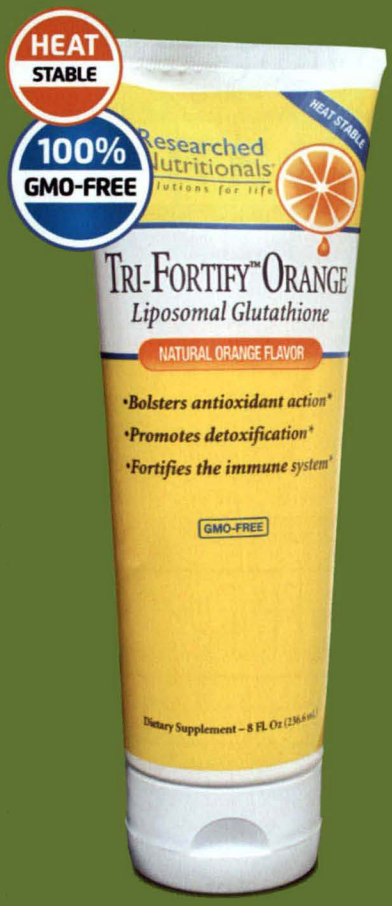

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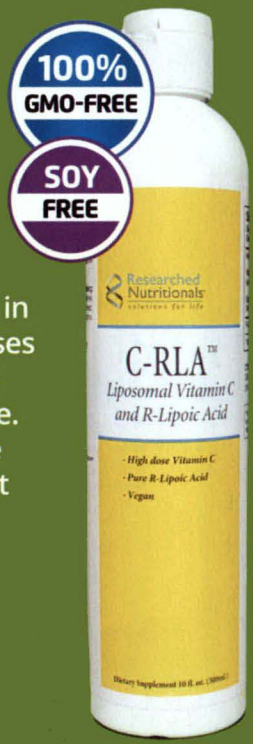

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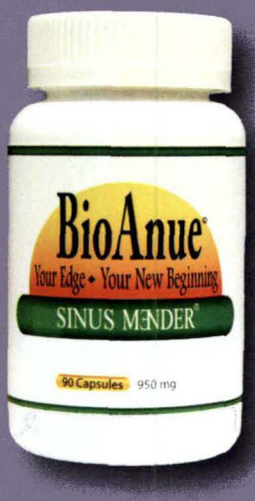

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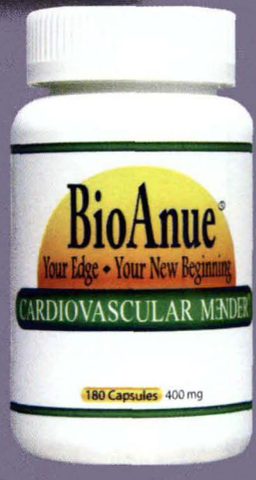

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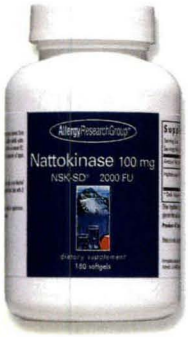

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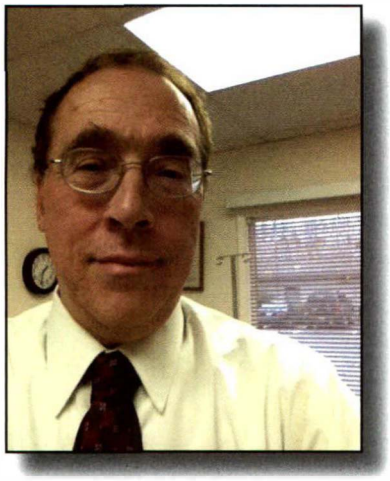
1. Agadjanyan M, Vasilevko V, et al. J Chronic Fatigue Syndr 2003;11(3):23-26. - 2. Ellithorpe RR, Settineri R, et al. J Am Nutraceut Assoc 2003; 6(1):23-28.
3. Ellithorpe RA, Settineri R, et al. Funct Food Health Dis. 2011;1(8): 245-254. - 4. Nicolson GL, Ellithorpe R, et al. J Am Nutraceut Assoc. 2010;13(1):10-14.



From the Publisher

Alternative Medicine Critics Trash Chelation and TACT

You know the "gotcha" line – "Heads, I win ... tails, you lose." Alternative medicine critics – arrogant medical school faculty, self-serving medical board members, and professional self-appointed quack-busters – like this "heads/tails" game. When the study demonstrates the alternative modality doesn't work, it proves their point; when the study shows the integrative modality works, then there's something wrong with the study. When the alternative treatment doesn't work and the patient doesn't improve, it proves their point; when the treatment works and the patient improves, it wasn't the treatment, it was the doctor's bedside manner, diet and exercise, placebo. From the medical school faculty and the quack-buster's point of view, alternative medicine is unscientific, not evidence based, ineffective, a waste of money, interfering with the patient's obtaining appropriate medical care, and dangerous. I am not talking about the medical school and medical board viewpoint of the 1950s or 1980s – I am talking about what medicine thinks about alternative, naturopathic, integrative, functional, orthomolecular

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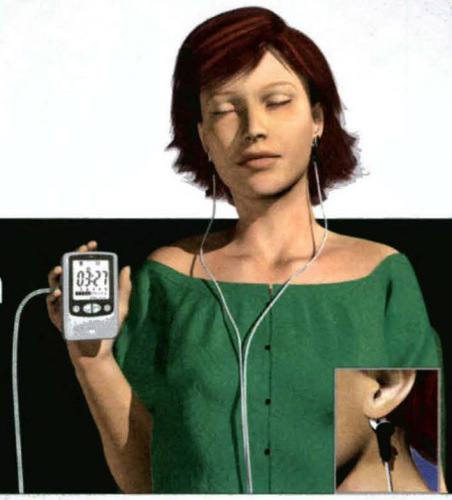

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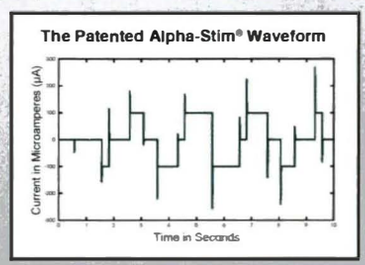

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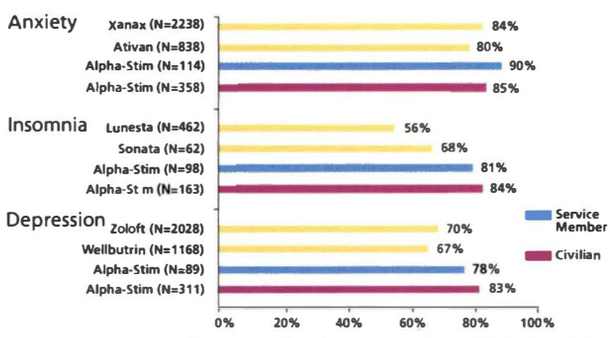

Patients who repor ed a positive response according to WebMD Drug Surveys, and Alpha-Stim Service Member and civilian surveys. Alpha-Stim Data from 2011 Military Service Member Survey (N=152) and Alpha-Stim Patient Survey (N=1,745). Conducted by Larry Price, PhD, Associate Dean of Research and Professor of Psychometrics and Statistics, Texas State University. Pharmaceuti al Survey Data from www.WebMD.com/drugs. Accessed on October 28, 2011.

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Letter from the Publisher
continued from page 6

medicine in 2014. Don't believe me? Search Wikipedia for the subject "alternative medicine." It is the consensus viewpoint of science and medicine in 2014 and it is not pretty. Despite all the accomplishments made in naturopathic and functional medicine over the past three decades, the scientific and medical communities disdain alternative medicine. It is time that the alternative medical community pick up their "swords" and attack the critics and naysayers.

The NIH-sponsored TACT (Trial to Assess Chelation Therapy), conducted over nine years, demonstrated a positive outcome in the prevention of heart attack, stroke, and death in patients having diabetes and myocardial infarction. This was a randomized, blinded study published in *JAMA* – just what the critics wanted – and the positive result was rejected not just in editorials but also on the page discussing "Chelation Therapy" in Wikipedia. The "open-minded" cardiologist might think that chelation offers risk protection that is wholly unique to medicine – no drug or surgical intervention is capable of offering a similar risk reduction for a cardiovascular event. This means that chelation would increase the odds that a diabetic patient with a history of heart attack would benefit with prescribed medication, surgical intervention if needed, *and* chelation.

No one is arguing that chelation must be used instead of conventional therapy; instead it should be advised as an additional support. But the naysayers and critics won't have it. They actually claim that the study was rigged because it had research participants, doctors, who supported chelation and were members of societies that advocated chelation. TACT principal investigator Gervasio A. Lamas, MD, ended the report with a statement that the trial cannot recommend chelation for implementation without further study. Nevertheless, given the succession of a few small university-based chelation trials that had negative outcomes, the largest and longest randomized trial on chelation had a positive outcome and the naysayers want to condemn it as a fraudulent study! Chelation critics Kimball Atwood, MD, and David Gorski, MD, stated that "the final results of TACT, published in November 2012, showed no support for the use of chelation therapy in coronary heart disease, particularly the claims to reduce the need for coronary artery bypass grafting" (Wikipedia, "Chelation Therapy"). Of course, that was not the purpose of TACT, and the study did indeed support the use of chelation therapy in coronary heart disease. Readers should review the December 2013 *Townsend Letter* interview of Lamas by Kirk Hamilton.

continued on page 15 ➤

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Serving Size: 20 drops
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Amount Per Serving	%Daily Value
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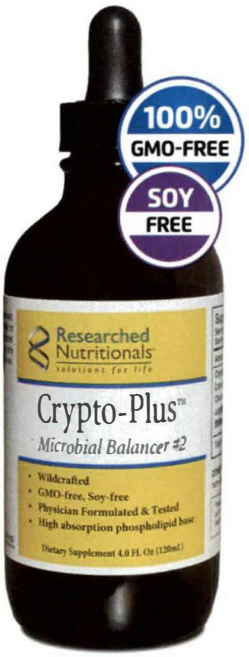
Juglans Nigra (Black Walnut hulls)	*
Stillengia Sylvatica	*

*Daily Value not established.

OTHER INGREDIENTS: Organic alcohol, distilled water, non-GMO sunflower phospholipids.



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Letter from the Publisher

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In 2008 Atwood (anesthesiologist at Tufts University and editor of *Scientific Review of Alternative Medicine*), Elizabeth Woeckner (litigator for medical boards), Robert Baratz, MD, DDS, PhD (expert witness for medical board disciplinary litigation), and Wallace Sampson, MD (professor of medicine and editor-in-chief of *Scientific Review of Alternative Medicine*), authored a 89-page editorial epic titled "Why the NIH Trial to Assess Chelation Therapy (TACT) Should Be Abandoned" (*Medscape J Med.* 2008; 10[5]:115). The *Scientific Review of Alternative Medicine* is a journal of review articles that purportedly demonstrates the failure or inefficacy and danger of alternative therapies. Hence, it is not surprising that Atwood, Woeckner, Baratz, and Sampson would author a highly scathing report about TACT, chelation, and the study's investigators. The authors employ, to borrow a Civil War term, a "scorched earth" approach to denigrate the science of chelation therapy and its proponents. For those doubting Thomases who think that my call to arms is unwarranted, please take an hour or so and wade through this document – not only do the authors tear apart every positive chelation study, but they also find every means to debase individual chelation doctors (yes, chelation doctors – you have the dubious honor of having your practices and public records discredited).

This is from the abstract of Atwood et al.:

> We have investigated the method and the trial. ... We present evidence that chelationists and their organization, the American College for Advancement in Medicine, used political connections to pressure the NIH to fund TACT. The TACT protocols justified the trial by misrepresenting case series and by ignoring evidence of the risks. The trial employs nearly 100 unfit co-investigators. It conflates disodium EDTA and another, somewhat safer drug. It lacks precautions necessary to minimize risks. The consent form reflects these shortcomings and fails to disclose apparent proprietary interests. The trial's outcome will be unreliable and almost certainly equivocal, thus defeating its stated purpose.

Wikipedia ("Chelation Therapy") cites Atwood et al.'s conclusion that "the proposed study has been criticized as unethical, unnecessary and dangerous, with multiple studies conducted in the past demonstrating that it provides no benefit."

Isn't it ironic that this unnecessary and dangerous study found that there was an overall 18% reduction in risk in having a cardiovascular event in the chelation group compared with the placebo group? TACT demonstrated that in the group of patients who had sustained prior to the study a large anterior wall myocardial infarction, a very vulnerable heart-disease population, there was a 40% reduction in risk in having a future major cardiovascular event. This is a potential benefit that current cardiac drugs are not capable of providing. Yet, Atwood and Gorski state that the study demonstrates no benefit for cardiac disease.

Yes, "Heads, I win ... tails, you lose." The medical community "knows" that chelation doesn't work and is dangerous. The fact that TACT found minimal adverse events in the chelation treatment group can't be true. The fact that TACT found significant risk reduction in cardiovascular events in the treatment group can't be true. The only thing that matters is the few studies that demonstrated chelation failure and the editorial comments of the critics and naysayers.

FDA Clamps Down on Compounding Pharmacies

In 2012 a large number of patients developed fungal meningitis or a related fungal disorder as a result of being treated by a contaminated compounded steroid drug. The adulterated injectable was primarily manufactured by one pharmacy near Boston, the New England Compounding Center. Although the facility had been criticized and sanctioned by Massachusetts's pharmacy authorities during the previous five years, it had been able to continue making and distributing drugs to hospitals and clinics with impunity. Inspections had revealed that not only had the manufacturer failed to maintain sterile rooms, but drugs were made in the proximity of debris and contaminated materials. As a result of many patients' dying or requiring extensive treatment for resistant fungal infections, there was a public outcry for policing of compounding pharmacies. Congress could agree on little in 2013 but easily managed a bipartisan vote to direct the FDA to police compounding pharmacies. After Obama signed the legislation into law, the FDA did not waste time implementing the Compounding Quality Act. The FDA set up deadlines for a comment periods on the act – a March 4 deadline has now passed for comment on a section known as "Nomination for Lists" (of drugs that may or may not be compounded). Compounding pharmacies face a deadline of Oct. 1, 2014, to file an application to become an "outsourcing facility" (permitting the facility to compound a drug without needing to comply with drug manufacturing requirements). There is the distinct possibility that some and perhaps most compounded prescriptions will not be filled after Oct. 1. For those clinics and physicians who administer injectable chelation, vitamins, minerals, amino acids, herbals, and other nutraceuticals, this may mean that these injectables will be completely unavailable from compounding pharmacies and injectable manufacturers. For those clinics administering hormone therapies, there is the possibility that only brand-name and generic pharmaceutical hormones will be available; customized hormone prescriptions may be banned. What will be available and what will not be available will depend on whether the "drug" or "bulk substance" is approved on the FDA list of acceptable compounded drugs.

The rules of acceptance for compounding a bulk drug are:

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Letter from the Publisher
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1. The bulk drug substances comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph, if one exists;
2. If such a monograph does not exist, the drug substance(s) is a component of an FDA-approved human drug product; or
3. If such a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it appears on a list of bulk drug substances for use in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FDCA).[1]

Furthermore, according to Section 503B, an "outsourcing facility may only compound with a bulk drug substance which appears on the FDA-established list of bulk drug substances for which there is a clinical need or which are on FDA's drug shortage list." Given the scare interest if not derision in the medical community regarding IV chelation and nutrient therapy, does it seem likely that the FDA will deem that injectable components have "a clinical need?"

Furthermore 21 CFR 216.24 asserts that there will be "a list of drugs that may not be compounded because they have been withdrawn or removed from the market because the drugs or components of the drugs have been found to be unsafe or not effective. Compounders may not compound any drugs that appear on this list." Hence, many compounded prescriptions will be banned because the FDA will be listing the drugs as "unsafe" or "ineffective." Physicians who prescribe compounded prescriptions will find their hands tied with these regulations. Clinics administering IV therapies will be very limited because the majority of IV components are only available through compounding. Patient prescriptions will not be filled or renewed due to the FDA policies.

It is unclear how we should approach the FDA to ensure that injectables, hormones, and other compounded substances will be approved for compounding. Efforts at approaching legislators and the general media have not been effective – the public consensus has been that because of the NECC fiasco, compounding pharmacies must be reined in and policed. While a compounding pharmacy may apply to be an "outsourcing facility," the onerous requirements of the state pharmacy board and FDA inspections may prove to be too difficult and expensive. Additionally the FDA authorized a "Memorandum of Understanding between the FDA and the States (MOU)" that requires that there may not be an "inordinate amount" of interstate compounded prescribing. The FDA is proposing that compounders may not send more than 5% of their compounded prescriptions across state lines. In addition to the administrative nightmare of limiting interstate compounding to 5% of their prescriptions, pharmacies would not be able to afford making injectables without being able to do business with out-of-state clinics. Furthermore, a compounding pharmacy making injectables requires a certified sterile facility – a financial and manufacturing commitment exceeding the capabilities of most compounding pharmacists.

All clinicians and practitioners who use injectables or prescribe compounded hormones should confer and strategize with their compounding pharmacist about the FDA implementation of the Compounding Quality Act. Waiting until the FDA takes action will be too late!

Jonathan Collin, MD

Resources

1. FDA implementation of the Compounding Quality Act [Web page]. http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm375804.htm.
2. Compounding and the FDA: questions and answers [Web page]. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm.
3. Text of Compounding Quality Act [online document]. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm.

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In Memoriam:
James Puckette Carter, MD, DrPH, MS

When you've been a part of integrative medicine's history for over 30 years, it's sobering to look back and recall when you first started – I looked up to docs who had been doing chelation and such for 5 years or 8 years and thought that they had more experience than anyone!

Now I'm one of the graybeards, and I am saddened to take this opportunity to acknowledge the passing of one of *my* mentors for most of those years of my learning, Jim Carter.

Like the rest of us, he earned a medical doctorate – then he went far beyond, authoring dozens of professional articles and guiding many of us along our inquiries into how the body works and how our treatments can be made *most* effective.

He forever worked tirelessly to introduce our way of thinking into the hallowed halls of academe – and he was equally committed to having *us* understand the best ways to adopt latest scientific discoveries into our practices.

Our rich friendship was filled with times when he never failed to offer assistance and counsel, and I was one of many who enjoyed his personal attention. His beloved wife, Carolyn Harris, patiently encouraged the time and energies that he devoted to us, his friends, and to our passion, our kind of health care.

He presented lectures and impromptu commentaries to us many times. His style was simple: take the basic science facts, combine them with an advanced understanding of human physiology, and weave these into a rich tapestry that clearly displayed the future of nutritional chemistry in the prevention and treatment of human ailments.

And he shared these ideas not just with us but with his many medical and graduate students at Tulane School of Medicine, where he served for many years as professor of pediatrics and chief of the section on nutrition.

Trained at Northwestern and Columbia Universities, he served on the faculty at Vanderbilt and Meharry. *And* as a consultant to the World Health Organization, the National Academy of Sciences, and the Agency for International Development and as an editorial adviser to *Prevention* magazine.

His list of accomplishments is too long for recitation here, but note that he was one of only a few dozen to receive a Faculty Fellowship from the Milbank Memorial Fund to develop a professional career as a medical educator in nutrition – and *that* was over 45 years ago!

We have long been blessed to enjoy his strong leadership on the ICIM (International College of Integrative Medicine) scientific review board, our institutional review board, our board of directors. In 1988, he was elected to life membership in our organization and appointed as research adviser to our board. He also helped then to plan the first FDA-approved study of chelation, which was aborted by the first Gulf War.

In 1990, he coauthored a landmark double-blind study on chelation in peripheral vascular disease, published in the *Journal of the National Medical Association* – no other major journal would touch this politically hot topic. Those of you who have not read his superb book, *Racketeering in Medicine*, have missed a critical part of *our* history – read it next week!

In 2008, his many achievements led to this ICIM Distinguished Lifetime Achievement Award to James Puckette Carter, our friend, mentor, and colleague: " ... in recognition of his devoted efforts to further research, understanding, and application of innovative strategies to advance human health through nutrition and pharmacology and his tireless commitment to merge the finest perspectives from the hallowed halls of academe and the pragmatics of private practice."

Dr. Carter had retired from Tulane to offer chelation therapy and nutritional medicine in his office in New Orleans until Hurricane Katrina took both his clinic and his home. He relocated north of the lake, to Mandeville, where he had continued his active participation in the TACT study on chelation and his gentle practice. James Puckette Carter departed this life on February 13, 2014, succumbing to complications of illness.

Jim – you touched our hearts as well as our minds – we will carry forward your lessons and inspiration in our lives and practices.

– One of Dr. Carter's thousands of students

ICIM's $20,000 Commitment to Chelation Research

The International College of Integrative Medicine (ICIM) grew out of a physician study group in the Great Lakes region led by Jim Nutt, DO, in the 1970s. ICIM's signature therapy is EDTA chelation for vascular disease. Semiannual meetings feature prominent speakers that teach a variety of integrative techniques that members can use in their practices immediately. Members come from the US and around the world.

James P. Carter, MD, a professor at Tulane University's School of Public Health, helped the group define its commitment to educating its members and staff, protecting their ability to practice innovative medicine, and stimulating meaningful research. For many years, Dr. Carter led ICIM's Scientific Advisory Committee and IRB. A remarkable number of office-based research projects by members came out of these efforts. ICIM doctors often contribute articles to the *Townsend Letter*.

ICIM members testified at Dan Burton's congressional hearing that eventually led to NIH funding of the Trial to Assess Chelation Therapy (TACT), and several became investigators in the study. When the positive results of TACT were presented and published, ICIM held a summit meeting to discuss and make recommendations about what the next step should be to bring chelation therapy into generally accepted use.

It is clear that another study is required to confirm the results of TACT for treating vascular disease and diabetes. Ethical concerns about the use of placebos were expressed at the summit by doctors who have seen the

ICIM Offers $20,000 Prize to the Best Proposal to Advance Chelation Research for Cardiovascular Disease

The International College of Integrative Medicine (ICIM) is offering a grant of $20,000 to stimulate further research on chelation therapy to treat vascular disease and/or diabetic complications. The funds are to be used to plan a significant study. Applicants must submit an adequate explanation of their proposals to include 1) the likelihood of a successful outcome based on previous studies, 2) the possibilities for funding of the entire study, and 3) involvement of experienced researchers and clinicians.

Proposals should be no more than 2–3 typewritten pages. They can be submitted to wendy@icimed.com by email. The deadline for proposals is 31 May, 2014. The Grant will be called the James P. Carter Memorial Grant for EDTA Chelation Research.

The International College of Integrative Medicine is a community of dedicated physicians who advance innovative therapies in integrative medicine by conducting educational conferences, supporting research, and cooperating with other scientific organizations, while always promoting the highest standards of practice.

ICIM's Summit on the Future of Chelation Therapy, Washington, DC, March 2013

benefits of chelation. Physicians knowledgeable about chelation therapy are likely to know which diseases are most amenable to treatment. There is concern that opponents of the therapy could put together a follow-up study that is "designed to fail."

Recognizing that it takes considerable work to plan a major research project, the ICIM board of directors decided to call for proposals for a $20,000 grant to be used for this purpose. Anyone is welcome to apply. The board wants to stimulate innovative thinking for projects that include both experienced clinicians and talented researchers.

The ICIM board dedicates the grant to Dr. Carter, who recently died and whose contributions to the acceptance of chelation therapy are immeasurable.

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Request for Proposals for Chelation Research

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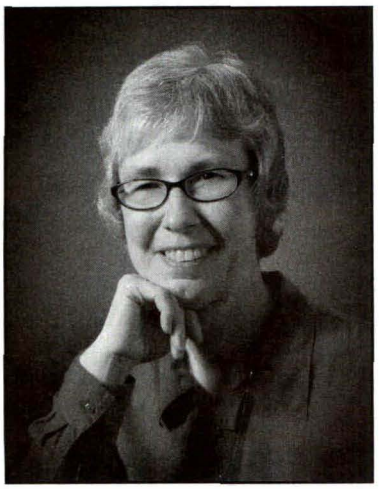

Shorts

briefed by Jule Klotter
jule@townsendletter.com

2013 Statin Guidelines

People with LDL cholesterol levels of ≥130 mg/dL should not take statin drugs if that is their only risk factor for cardiovascular disease, according to new guidelines developed jointly by the American Heart Association, the American College of Cardiology, and the Obesity Society. The expert panels that produced the November 2013 guidelines could not find evidence that lowering LDL levels to a targeted level reduces heart attack or stroke risk, according to a *New York Times* article by Gina Kolata. Instead of focusing on LDL cholesterol, the new algorithm uses gender, age, race, HDL and total cholesterol levels, diabetes, hypertension, systolic blood pressure, and smoking as the variables to determine cardiovascular risk (See ASCVD Risk Estimator in references, below). In addition, the guidelines have lowered the bar for when to begin statin treatment – a decision that has drawn heavy criticism from practitioners.

Instead of a 10% to 20% risk of a cardiovascular event within 10 years, the new algorithm says, anyone with just a 7.5% to 9.9% risk within 10 years needs statin therapy. "'According to the new risk calculator all African American men aged 65 and up with normal blood pressure and normal cholesterol levels should be on statins," cardiologist Barbara Roberts told the *British Medical Journal* (*BMJ*). "That's an outrage and is unsupported by clinical evidence.'"

The risks of statin therapy may outweigh benefits for many patients – a factor that the guidelines panel did not consider, according to David Newman, a physician researcher at Mount Sinai in New York City. Newman told the *BMJ*: "'For patients without diabetes or a prior heart attack or stroke who are treated with statins for five years, 98% will see no benefit: 1.6% will be spared a heart attack and 0.4% a stroke – and importantly, there will be no difference in overall mortality. At the same time, 2% of individuals treated with statins will develop diabetes and 10% will have muscle damage.'"

Roberts and Newman are not the only critics. John D. Abramson, a Harvard Medical School lecturer, and Rita F. Redberg, cardiologist and editor of *JAMA Internal Medicine*, wrote a blistering editorial criticizing the new recommendations for "expanding the definition of who should take the drugs – a decision that will benefit the pharmaceutical industry more than anyone else." They point out that the American College of Cardiology and the American Heart Association both receive major funding from drug companies. "Statins are effective for people with known heart disease," they write. "But for people who have less than a 20 percent risk of getting heart disease in the next 10 years, statins not only fail to reduce the risk of death, but also fail even to reduce the risk of serious illness. ..."

Moreover, Abramson and Redberg worry that patients will be content to take medication instead of making lifestyle changes that provide true prevention of cardiovascular disease. Smoking, lack of exercise, poor diet, stress, and other lifestyle factors cause 80% of cardiovascular disease. "Statins give the illusion of protection to many people, who would be much better served, for example, by simply walking an extra 10 minutes per day," say the authors.

Eight of the 15 panel members who drew up the guidelines – including the chairman and one of two cochairs – had ties to the pharmaceutical industry, according to a *BMJ* article by Jeanne Lenzer. Neil J. Stone, the panel's chairman, had financial ties to Abbott, AstraZeneca, Merck, Pfizer, Sanofi-Aventis, and Schering-Plough when asked to lead the panel; all six companies make cholesterol-lowering drugs. He told *BMJ*, "I immediately severed ties with all industry connections prior to assuming my role as chair." Jerome Hoffman, professor emeritus of medicine at the University of California, Los Angeles, told Lenzer "'... unless the decision to sever financial ties represents a fundamental change of heart – and is accompanied by an absolute pledge not to take money from industry in the

continued on page 25 ➤

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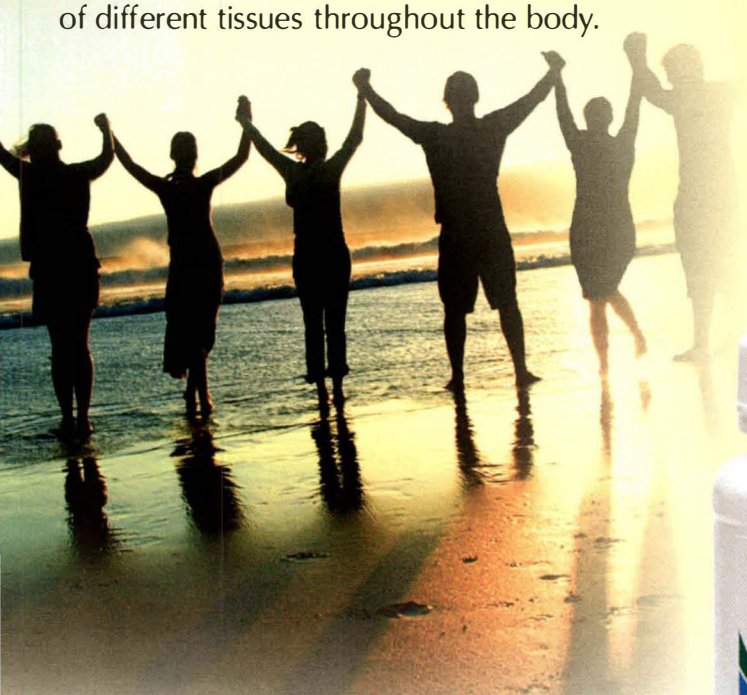

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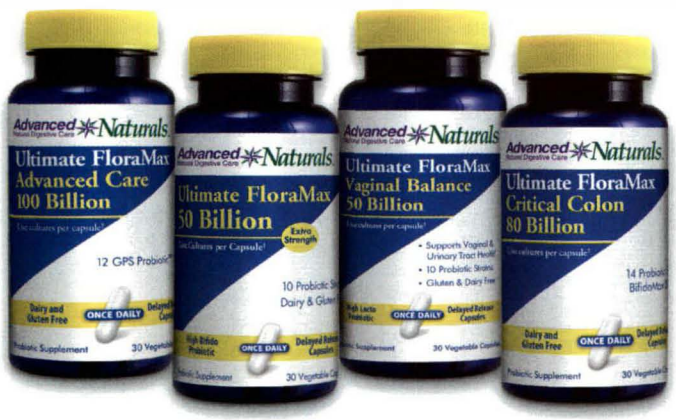

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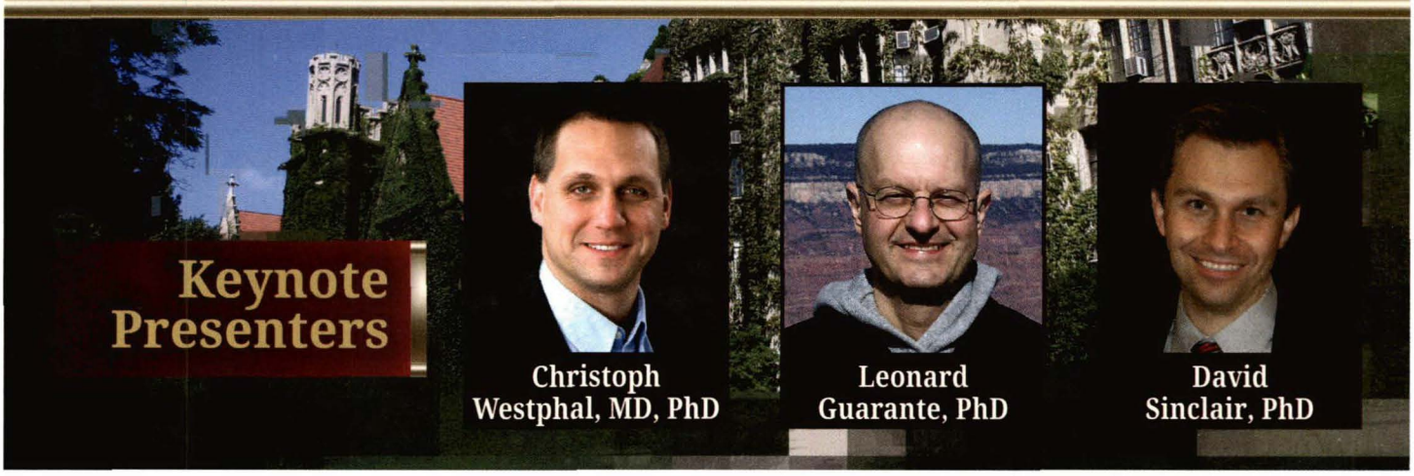

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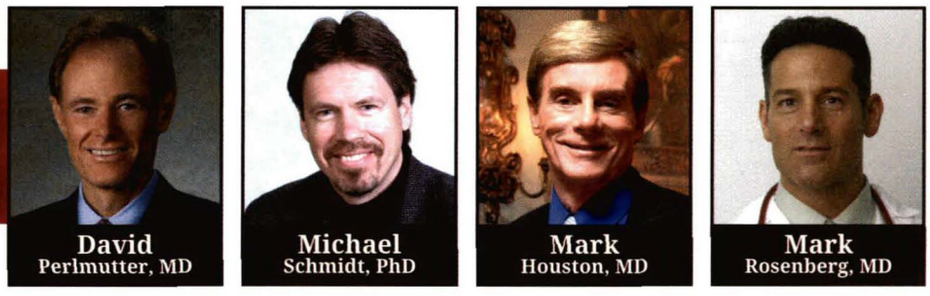

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➤*continued from page 20*

future – this type of revolving door relationship between 'public service' and [industry] is about as clear a model of conflict of interest as I can imagine.'" Stone told *BMJ* that he would not accept industry funding for two years after the guidelines were released.

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Homeopathy and Asthma

Individualized homeopathic treatment reduced children's asthma severity and need for conventional medications in a small 2012 observational study led by H. F. Shafei. Thirty children with diagnosed asthma, aged 7 to 15, took part in the study. Asthma severity and bronchodilator and/or corticosteroid inhaler use were stable in the year before the children were referred to pediatricians at Egypt's Homeopathic Clinic of the National Research Center (Cairo), according to Christopher Johnson, ND.

In addition to standard medications, children received homeopathic medicine that best matched their individual physical symptoms and mental-emotional expression. They were given a single dose of a polychrest in 200c potency and a "respiratory remedy" for daily use. Because polychrests affect numerous physical, emotional, and mental aspects, they are often used to support a person's overall constitution. In this study, *Calcarea carbonicum* and *Natrum muriaticum* were the two most frequently prescribed polychrests. Both are associated with coughing and shortness of breath, but the personality profiles differ. *Calcarea carbonicum* is appropriate for children who tend to be obstinate and worry about their health and safety. *Natrum muriaticum* is the remedy for children who are hypersensitive to reprimands and want to be left alone when they don't feel well. In contrast to the constitutional remedy, the respiratory remedy was in a lower potency (up to 30c) and taken daily to address coughing episodes. These remedies were chosen based on symptoms such as coughing triggers, associated pain, sound of the cough, type of mucus (if any), and time that coughing most often occurred.

After 6 months, the researchers assessed the effect of adjunctive homeopathic therapy by comparing asthma medication use and symptom frequency with baseline measures. At baseline, 33% of the children (n = 10) used inhalers more than once a day; 20% (n = 6) used them once a day; 40% (n = 12) used them 2 to 6 times a week; and 7% (n = 2) used them less than twice a week. "After 6 months of treatment," writes Johnson, "not a single child was using their inhaler throughout the day and only 6% used inhalers even once a day." Oral corticosteroid use also fell. Ninety percent of the children (n = 27) needed more than two courses of oral corticosteroid therapy a year before homeopathic treatment, compared with just 10% (n = 3) after treatment.

Symptoms also declined. At baseline, 30% of the children experienced asthma symptoms every day with an addition 23% experiencing symptoms "'throughout the day.'" By study's end, only 7% had daily symptoms. None had symptoms that bothered them all day long. The only adverse event was "'the appearance of transient skin papules which disappeared in 24 hours... after improvement of asthma symptoms.' Most homeopaths would view this as an "aggravation" of symptoms and a positive sign of healing," says Johnson.

The next step, according to the Egyptian authors, is placebo-controlled study. (I hope these controlled studies, like this one, involve experienced homeopathic doctors.) Although they can save lives, conventional asthma medications have adverse affects, such as adrenal insufficiency, decreased growth, weight gain, delayed puberty, and hyperactivity. Competent homeopathic treatment could lessen the need for the drugs and, thereby, reduce children's exposure to these risks.

Johnson C. Asthma on the rise. ... *Homeopathy Today*. Spring 2013;36–37.

Shafei HF, AbdelDayen SM, Mohamed NH. Individualized homeopathy in a group of Egyptian asthmatic children [abstract]. *Homeopathy*. October 2012; 101(4);224–230. Available at www.ncbi.nlm.nih.gov/pubmed/23089218. Accessed March 3, 2014.

Clogged Plumbing and Heart Stent Overuse

"Although the image of coronary arteries as kitchen pipes clogged with fat is simple, familiar, and evocative, it is also wrong," says Michael B. Rothberg, MD, MPH, in a 2013 commentary. That image, however, has led to the overuse of heart stents, small metal mesh tubes that are inserted in an artery, during angioplasty. Using a heart stent to hold open and strengthen a blocked coronary artery can be lifesaving during a heart attack; but the procedure does not prevent heart attacks in people with stable cardiovascular disease – a fact that most patients and some doctors do not realize.

As Rothberg points out, cardiovascular disease is not a plumbing problem that can be solved with a surgical Roto-Rooter. Angioplasty and heart stents address distinct constrictions or blockages in an artery. These procedures, however, do not address inflammatory damage that is occurring in other parts of the artery, damage that weakens vessels and can lead to rupture. In most cases, cardiac events occur at weakened areas that show little evidence of blockage. "Before rupture," says Rothberg, "these plaques often do not limit flow and may be invisible to angiography and stress tests. They are therefore not amenable to percutaneous coronary intervention [angioplasty]."

Still, 9 out of 10 patients undergoing elective angioplasty believe that the procedure will prevent future cardiac

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events, according to a small study conducted by Rothberg and colleagues. This erroneous belief is largely cultivated by the "old plumbing analogy" still used in advertisements and educational materials. Rothberg suggests a different analogy to help patients understand cardiovascular disease. He says that cholesterol deposited in arterial walls produces "an inflammatory reaction, like a pimple." "When those pimples pop, they cause the blood in the arteries to clot at the site," he explains. "If the clot closes off the entire artery, that causes a heart attack, and emergent medical attention is required to remove the clot." Sometimes, old plaques, "like scarred old pimples," partially block blood flow, producing pain. If medication does not relieve the pain, angioplasty is the next option for symptom relief.

Reducing inflammation through evidence-based lifestyle changes (smoking cessation, exercise, stress reduction, and a Mediterranean diet) and anti-inflammatory medications are the "only effective measures" for preventing heart attacks, says Rothberg. Nonetheless, he expects the plumbing analogy and angioplasty overuse to continue, "... partly because it is difficult to admit that in the past we got it wrong and performed what now appear to have been unnecessary procedures, but also because our current payment system continues to reward interventions based on the old model and cardiac procedures are an important source of hospital revenue." The average cost of angioplasty is about $30,000, according to *New York Times* reporter Anahad O'Connor.

Rothberg MB. Coronary artery disease as clogged pipes: a misconceptual model. *Circulation.* 2013;6:129-132. Available at http://circoutcomes.ahajournals.org/content/6/1/129. Accessed February 14, 2014.

O'Connor A. Heart stents still overused, experts say. *New York Times.* August 15, 2013. Available at http://well.blogs.nytimes.com/2013/08/15/heart-stents-continue-to-be-overused. Accessed February 6, 2014.

Soil, Microbes, and Allergies

Tiny organisms living in the earth's soil are the linchpin for health in all life forms. For humans, the benefits extend far beyond the hygiene hypothesis, or "farm effect," which posits that exposure to diverse organisms makes our immune systems less likely to overreact and produce allergic responses. Scientists are just beginning to identify microorganisms (bacteria, viruses, fungi) and parasites in the natural environment that interact with larger life forms (including humans) to their mutual benefit. This ecological viewpoint is reflected in the biodiversity hypothesis, an extension of the hygiene hypothesis.

The biodiversity hypothesis says that the less contact people have with a microbially diverse natural environment, the less diverse their own commensal microbiota. Commensal organisms produce molecules that activate health-supporting biochemical responses in their hosts, including immune modulation. Many people in over-developed nations live in microbially poor environments. Urbanization and disruption of soil habitat with chemicals and plowing reduce microbial diversity. Allergies and other inflammatory illnesses are most common in industrialized countries.

Ilkka Hanski and his colleagues at the University of Helsinki (Finland) published a 2012 study that supports the biodiversity hypothesis. The researchers took a random sample of adolescents living within a 100 by 150 km area (62 by 93 miles) and looked at allergy incidence, microbial diversity in the yards around their homes, and microbes living on their skin. They made three discoveries. First, the bacterial classes on the teens' skin reflected the diversity in their yards. Second, healthy teens had greater diversity surrounding their homes and significantly higher generic diversity of gammaproteobacteria on their skin compared with teens who had allergies. Third, gammaproteobacteria, specifically *Acinetobacter*, "positively correlated" with the expression of interleukin-10 in the teens' blood mononuclear cells. IL-10 is "a key anti-inflammatory cytokine in immunologic tolerance," according to the authors.

Acinetobacter and other organisms may produce the same anti-inflammatory effect when they are inhaled, according to Graham Rook, professor emeritus of medical microbiology at University College London. "'We do not know the relative importance of contact via the skin and via the airways,'" he told Sharon Levy, writing for *Environmental Health Perspective,* "'but physiologically the airways seem more likely.'"

The Finnish team noticed a direct correlation between the diversity and abundance of bacteria on teens' skin and the presence of native plants in their yards. Native plants have coevolved with indigenous microbes, insects, and other life forms, forming an interdependent community – much like the organisms living in and on our bodies. "[It] is the cooperation between bacteria, fungi, and plants' roots (collectively referred to as the rhizosphere) that is responsible for transferring carbon and nutrients from the soil [and air] to the plant – and eventually to our plates," says Daphne Miller, MD, author of *Farmacology: What Innovative Family Farming Can Teach Us About Health and Healing.* The key to inflammatory disease may lie in the health of our soil.

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Levy S. Reduced bacterial biodiversity is associated with increased allergy. *Environ Health Perspect.* August 2012;120(8):A304. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3440091.

Miller D. The surprising healing qualities ... of dirt. *Yes!* Winter 2014. Available at www.yesmagazine.org/issues/how-to-eat-like-our-lives-depend-on-it/how-dirt-heals-us. Accessed February 6, 2014.

Grounding (Earthing) and Blood Viscosity

Grounding; that is, physically connecting to the earth's electron field, reduces blood viscosity and aggregation by changing the electrical surface charge (zeta potential) of red blood cells (RBC), according to a study led by Gaétan Chevalier, PhD, at University of California, Irvine. During grounding, electrons from the earth enter the body and increase the RBC surface charge. "A higher repulsive

surface charge," the authors explain, "increases spacing between erythrocytes, reduces clumping, lowers viscosity, and lowers peripheral resistance to flow."

Both the human body and soil (unless it is extremely dry/desert) conduct electrons. Chevalier and colleagues explain, "... when two conductive objects with different electrical potential touch each other, there is a virtually instantaneous transfer of charge so that the two objects equilibrate to the same electrical potential. ... " Whenever we lie on the grass or walk barefoot along a beach, the electrons from the earth's surface sweep into our bodies. In industrial cultures, most people have minimal contract with this natural bioelectric environment in which humans evolved. We no longer sleep on the ground. We spend much of our time indoors. And when we are outdoors, we are often wearing nonconducting rubber-soled shoes.

For their 2013 study, Chevalier and colleagues recruited 10 healthy people. Each person had a single 2-hour grounding session during which conductive patches, wired to a steel rod stuck in ground outdoors, remained on the soles of their feet and the palms of their hands. The absolute value of zeta potential increased in all 10: "The smallest absolute increase was by a factor of 1.27 and the largest was by a factor of 5.63." The person with the smallest increase lived on a raw-food diet, ran three times per week, and did yoga twice a week outdoors and at home. Overall, the average zeta potential increased "from a very small average value of ~5.28 mV into a normal value (~14.3 mV)." RBC aggregation also declined. After grounding, the researchers observed significantly more single red blood cells and two-celled clusters and fewer clusters of three or more cells. Blood pressure was not measured in this experiment.

Connecting with earth, whether directly or via wired conductors, has a positive effect on cardiovascular health. In addition to improved blood viscosity and aggregation, grounding improves heart rate variability and increases parasympathetic activity, according to previous research. And, the authors say, it is "virtually harmless." The only caveat is to monitor people taking blood-thinning drugs (e.g., warfarin) as frequent grounding sessions can change their medication needs.

Chevalier G, Sinatra ST, Oschman JL, Delany RM. Earthing (grounding) the human body reduces blood viscosity – a major factor in cardiovascular disease. *J Altern Comp Med.* 2013;19(2):102–110. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3576907. Accessed March 3, 2014.

Magnesium Deficiency and Cardiovascular Disease

Hypertension, high cholesterol, arterial calcification, and heart rhythm abnormalities are among the many signs of magnesium deficiency, according to Aileen Burford-Mason, PhD. Over 300 enzymes need magnesium in order to work properly – including the enzyme HMG-CoA reductase, which regulates cholesterol production. In addition, magnesium is a calcium antagonist and functions as nature's calcium channel blocker. "Calcium needs to rise in muscle cells for contraction to occur," Burford-Mason explains. "However before relaxation can follow, calcium must be shifted either outside the cell or back into storage sites within the cell. ... This process depends on the availability of magnesium." Without sufficient magnesium to relax smooth and cardiac muscles, people can experience hypertension, atrial fibrillation, and painful coronary and cerebral vasospasms.

Magnesium deficiency is very common, due to several factors. First of all, most Americans do not eat enough magnesium-rich foods such as pumpkin seeds, nuts, kelp, wheat bran, baking chocolate, and spinach. The actual content of these foods, however, depends upon the soil in which they grow. Carolyn Dean, MD, author of *The Magnesium Miracle,* says, "Magnesium is not a component of modern-day fertilizers. When plants have used up all the magnesium in the soil, unless it's replaced, there is none in the next crop." Another factor that contributes to magnesium deficiency is stress, including the physical stress of exercise. "Most human studies confirm that any form of exercise depletes magnesium. We sweat it out and stress it out and need extra magnesium to neutralize lactic acid," says Dean. Other causes of magnesium deficiency, according to Burford-Mason, include excessive urination associated with poorly controlled diabetes, excess alcohol consumption, and some prescription drugs including diuretics, proton pump inhibitors, and digoxin. The issue of magnesium deficiency is further complicated by individuals' genetic differences affecting the amount of magnesium required.

Blood tests do not give an accurate view of magnesium status because the body is continually shifting the mineral across membranes and from bone in order to maintain blood levels, says Burford-Mason. She recommends that practitioners look for functional evidence of a calcium/magnesium imbalance. In addition to the cardiovascular symptoms mentioned earlier, leg cramps or spasms,

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tight shoulder muscles, back spasms, muscle twitching around the eye, and restless leg syndrome are all signs of magnesium deficiency. "Imbalances will also be obvious in smooth muscle," she says, "resulting in physical signs of dysregulated lung function such as shortness of breath, wheezing or asthma [especially after exercise] and perhaps frequent sighing." Other signs include palpitations or irregular heartbeat, constipation, frequent urination at night, and nervous system symptoms such as anxiety, insomnia, fatigue, headaches, and irritability. If these symptoms are due to magnesium deficiency, they should improve with oral supplementation to bowel tolerance.

Burford-Mason recommends gradually increasing the dosage by 50 mg every three to four days until the person has one or two soft bowel movements per day. Too high a dose will produce diarrhea. She prefers to use amino acid chelates of magnesium (glycinate, aspartate, taurate) because they are not excreted from the kidneys as quickly as magnesium citrate.

Taking high doses of magnesium is not recommended for people with kidney disease (creatinine clearance < 30 mL/min) who are unable to eliminate excess magnesium.

Burford-Mason A. Orthomolecular medicine and heart health: unmasking the magnesium link to multiple risk factors for cardiovascular disease. *J Orthomol Med.* 2013;28(1):9–15. Available at EBSCO Database. Accessed February 14, 2014.

Dean C. *Magnesium.* El Segundo, CA: Active Interest Media Inc; 2011.

Autonomic Imbalance, Heart Failure, and Mind-Body Medicine

Sitaramesh Emani, MD, and Philip F. Binkley, MD, MPH, at Ohio State University (Columbus, Ohio) suggest that mind-body interventions that promote autonomic balance such as biofeedback, meditation, and relaxation techniques might benefit patients with chronic heart failure and reduce organ-damaging inflammation. Tai chi and yoga, which involve slow, focused movement and regulated breathing, also come under the category of mind-body interventions. Autonomic nervous system imbalance is characteristic of many stress-related conditions, including chronic heart failure. When sympathetic nervous function dominates and parasympathetic activity is low, pro-inflammatory cytokine production increases. These cytokines, in turn, promote norepinephrine production and sympathetic activity. The result is a self-feeding loop, promoting autonomic imbalance – unless the cycle can be broken.

Although mind-body interventions have improved cardiovascular risk factors in numerous studies, Emani and Binkley report that few studies have focused on patients with congestive heart failure. Most studies that they discuss in their article are small (< 100 participants) and short term, lasting 4 months or less. Nearly all of the studies found that mind-body intervention improved quality of life. Six-minute walking distance also increased in a most studies that used it as an outcome.

Unlike the studies in the Emani-Binkley article, a 2014 controlled study, performed by Bandi Hari Krishna and colleagues at Jawaharlal Institute of Postgraduate Medical Education and Research (Puducherry, India), measured inflammation and oxidative stress markers. These researchers found that yoga training as an adjunct to standard medical treatment had a significant positive effect on stable heart failure patients, with an ejection fraction of 30% to 50%. Patients with chronic obstructive pulmonary disease, orthopedic impediments, recent hospitalization (within 3 months), and myocardial infarction or recurrent angina (within 6 months) were excluded from the trial. Participants were randomly assigned to the yoga group (n = 44) or to the control group (n = 48), which received standard medical treatment without yoga therapy. For the first 2 weeks, patients in the yoga group attended a 60-minute yoga session (6 days per week), designed by a cardiologist and a yoga therapist. For the remaining 10 weeks of the study, patients practiced the routine in their homes for 3 of the 6 days each week.

Several oxidative stress and inflammatory markers were measured in all participants at baseline and at study's end. Total antioxidant status (TAOS), malondialdehyde (MDA), and redox ratio (a ratio for MDA and TAOS) were used to measure oxidative stress. Compared with baseline measurements, total antioxidant status increased 99.66% in the yoga group and 19.9% in the control after 12 weeks. Malondialdehyde, a marker of oxidation stress, declined 59.49% in the yoga group and 15.81% in the control. The redox ratio fell 77.19% in the yoga group and 20.59% in control.

Inflammatory markers also decreased more in the yoga group. High-sensitivity C-reactive protein fell 68.07% in the yoga group and 5.12% in the control group. Interleukin-6 decreased 33.96%, compared with 10.41% in the control; and tumor necrosis factor alpha decreased 31.02% in the yoga group and 14.79% in control. "The findings indicate that yoga training in addition to the standard medical therapy for [heart failure] patients was not only safe, but resulted in significant improvement in oxidative stress and inflammatory markers," the authors conclude. It would be

interesting to know if yoga had a rebalancing effect on the patients' autonomic function as well.

Emani S, Binkley PF. Mind-Body medicine in chronic heart failure: a translational science challenge. *Circ Heart Fail*. 2013;3:715–725. Available at http://circheartfailure.ahajournals.org/content/3/6/715.full. Accessed February 28, 2014.

Krishna BH, Pal P, Pal GK, et al. Yoga training in heart failure (NYHA 1-11) reduces oxidative stress and inflammation. *J Exerc Physiol*. February 2014:17(1). Available at www.asep.org. Accessed February 29, 2014.

Vitamin C and Stroke Risk

A 2013 meta-analysis, published in the *Journal of the American Heart Association*, found that long-term consumption of fruits and vegetables with high vitamin C content lowers stroke risk. Chinese researchers undertook the meta-analysis of prospective studies to evaluate the correlation between long-term low-dose consumption of vitamin C via diet, circulating C, and stroke risk. The Chinese research team included 12 prospective studies on vitamin C intake and 6 prospective studies on circulating vitamin C in the 2013 analysis.

The 12 dietary vitamin C intake studies involved 217,454 participants from Europe, Asia, and the US. The studies lasted between 6.1 years and 30 years, during which time a total of 3762 stroke events occurred. The high average C intake via diet varied among the studies from 45.6 mg/day to 375.8 mg/day. Two studies also measured supplement intake, reporting an average high of 850 mg/day from supplements alone in one study and 1120 mg/day in the second. About 20% fewer stroke events occurred in the group with the highest dietary intake of vitamin C compared with low-intake group; summary relative risk was 0.81 (95% CI: 0.74 to 0.90). Although average high intake levels were much greater in the studies with supplementation, the relative risk for those using supplements was about the same: 0.83 (95% CI: 0.62 to 1.10).

Instead of focusing on C intake, 6 studies measured serum or plasma vitamin C levels. Circulating C is considered a "good indicator of a diet rich in fruits and vegetables," say the authors. In these studies, the Chinese team followed a total of 29,648 participants (primarily European) for 9.5 to 20 years and documented 989 stroke events. The meta-analysis showed that people with high levels of circulating C had a 38% lower risk of stroke (RR = 0.62, 95% CI: 0.49 to 0.79) than those with low levels. Guo-Chong Chen and colleagues suggest that circulating vitamin C levels "may serve as a good predictor of stroke risk and diet status."

The authors point out that circulating vitamin C has a saturation point. At intake levels over 100 mg/day, "there is little change in blood concentration despite large changes in dose." Consequently, they do not expect supplementation to have much benefit for people whose diets produce high (saturated) blood concentrations of vitamin C.

Guo-Chong C, Da-Bing L, Zhi P, Qung-Fang L. Vitamin C intake, circulating vitamin C and risk of stroke: a meta-analysis of prospective studies. *J Am Heart Assoc*. 2013;2:e000329. doi:10.1161/JAHA.113.000329. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3886767. Accessed February 14, 2014.

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Pathways to Healing

by Elaine Zablocki

Researcher Finds Acupuncture Effective for Many Conditions

Karen J. Sherman, PhD, MPH, is a senior investigator at the Group Health Research Institute (GHRI) in Seattle. Her research interests include acupuncture, massage, meditation, and yoga. She's done studies on alternative therapies for anxiety disorders, back and neck pain, fibromyalgia, and menopause, as well as more general research on patient/provider interactions, communication and patient expectations.

Sherman has grown into this role through a series of transitions that will be familiar to many of us who are now middle-aged. When she first got her academic degrees, over 30 years ago, complementary therapies were not even part of the academic discourse. Sherman was fascinated with animal behavior, so she got a PhD in behavioral biology. She was also interested in human health, and went on to do postdoctoral work in epidemiology; she acquired a master's degree in that subject as well.

Sherman noticed that one of her mentors often studied the various products that her friends were using, and as a result did very creative research. "I thought that was an interesting way of doing things, because she was really relevant," Sherman recalled. "But I was 20 years younger, and my friends were more granola types, so they were doing and using very different things. I also began a meditation practice. This was back in the mid-1980s when, if there were scientists doing meditation, they were all in the closet."

But public perceptions of complementary therapies gradually shifted. In the mid-1990s, Washington State passed its "every category of provider" law and insurers were required to cover acupuncture. "That opened the door to doing research in this area," Sherman says. "In fact, Northwest Institute of Acupuncture (NIA) hired me as a research director." In the late 1990s, the National Institutes of Health/Office of Alternative Medicine began work to improve research in complementary therapies. While at NIA, Sherman worked on several research projects, some of them with Dan Cherkin of GHRI, and in 2001 she moved to Group Health as a full-time researcher.

Karen J. Sherman, PhD, MPH

Acupuncture Isn't Just One Thing

Traditional Chinese Medicine relies on a map of meridians and acupuncture points to determine the most effective places to insert needles. It often combines needling with herbal treatments, moxibustion/heat, and other therapies such as cupping or acupressure.

"Acupuncture has every type of conceptual challenge in doing research that you can imagine," Sherman says. "From the FDA perspective, testing therapies is all about medications, which are easier to study than other things because for many of them, you can make placebos." Conventional pharmaceutical research often compares a pill that has active ingredients with another pill that looks just the same but has no active ingredients. When researchers want to do comparable research on acupuncture, they face difficulties because Traditional Chinese Medicine is much more complex than taking a single pill. Treatment methods vary a great deal to meet the needs of each specific patient.

Researchers wanted to do rigorous research, so they developed studies that compared a "real" acupuncture point to a "sham" acupuncture point. Needles were used, but not on the traditional insertion points. "You know, acupuncture isn't just one thing," Sherman says. "Several styles of acupuncture are practiced today that don't involve actual needle insertion. When I was on staff at NIA, I listened to acupuncturists talk about how they practiced and why. Not all of them did needle insertion, and among those who did, some did deep insertion and some did shallow insertion."

As Sherman researched traditional acupuncture texts, she found that there are at least 100 points that can be recommended for back pain, and some of them are not on the meridians. In traditional texts, the point most often used for pain is called an Ashi point. "An Ashi point means that you palpate the body and wherever it's tender, you needle it," Sherman says.

The broad background of information on Traditional Chinese Medicine suggests that the sort of questions typically used in pharmaceutical research are not necessarily the right questions to ask when we look at acupuncture. "How can we compare a 'fake' acupuncture treatment to a 'real' acupuncture treatment when we don't really know how it works and thus cannot be sure the 'fake' treatment is really 'fake'?" Sherman asks.

At the same time, the best evidence that we have on acupuncture shows that it is effective in the real world for a wide variety of conditions. "Acupuncture is superior to usual treatment for a number of chronic pain conditions, including back and neck pain, osteoarthritis, and headaches," Sherman writes in a 2013 editorial in *Pain Management*. "Effects sizes are consistent with modest-to-moderate effects and are of clear clinical relevance. ... [In another study] acupuncture was both cost-saving and more effective than medications for prevention of migraines."

In 2005, Sherman and others wrote an article for the *Annals of Family Medicine* on the practice of acupuncture. The supplemental appendix to that article includes a marvelous overview of different practice styles in acupuncture, diagnostic techniques, types of needling, and adjunct treatments. The section on herbs and herbal safety is particularly valuable. These materials are available online (see Resources).

How Do We Find Appropriate Treatment?

There are many different styles of acupuncture, and no research makes head-to-head comparisons among the different styles. "Some traditional acupuncturists in our area have studied additional forms of acupuncture needling, such as trigger point therapy," Sherman says. "There are also acupuncturists in the United States who pick and choose among different styles. They might use a trigger point approach while figuring out what to needle, and then needle using a Japanese needling technique. British medical acupuncture is very scientific, but when it comes to picking out points in the peripheral areas, they pick them according to traditional acupuncture because empirically that works. You know, everybody swears by their own methods."

This means that choosing an acupuncturist, like choosing any other health-care professional, is a very personal matter. "The research offers us some guidance, but at a certain point you just have to go try it," Sherman says. "See whether it works for you, and see how you feel about the practitioner."

In addition to her work on acupuncture, Sherman has done considerable research on other complementary therapies such as massage and yoga. "The interesting thing is that many of the principles we observe in acupuncture turn out to be true for our other therapies as well," she says. "None of these are panaceas. The outcome you can usually expect is that you might be better for a while."

Responses to acupuncture, or yoga, or massage are variable and personal. "We've done a couple of large studies of yoga for back pain. Some people find they need to do yoga on a regular, frequent schedule. Others can go for long stretches, but when they get a flare-up then they need repeated sessions. No study is going to tell you about your own response. Over time, you have to discover what is going to work for you."

Resources

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Elaine Zablocki has been a freelance health-care journalist for more than 20 years. She was the editor of *Alternative Medicine Business News* and *CHRF News Files*. She writes regularly for many health-care publications.

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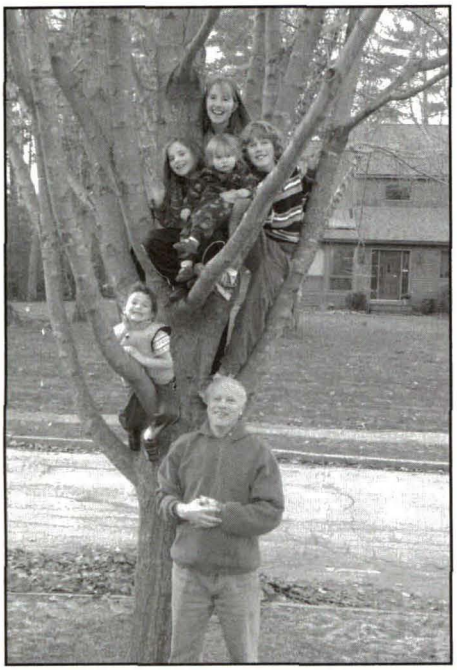

Literature Review & Commentary

by Alan R. Gaby, MD
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Flaxseed Lowers Blood Pressure

One hundred ten patients (mean age, 67 years) with peripheral arterial disease, 75% of whom had hypertension, were randomly assigned to receive, in double-blind fashion, various foods that provided daily 30 g of milled flaxseed or placebo foods for 6 months. After 6 months, mean systolic blood pressure was 9.4 mm Hg lower ($p < 0.05$) and mean diastolic blood pressure was 6.7 mm Hg lower ($p = 0.004$) in the flaxseed group than in the placebo group. The blood–pressure lowering effect of flaxseed was greater in patients with baseline systolic blood pressure ≥ 140 mm Hg than in those with lower levels. Body weight did not differ between groups at any time during the study.

Comment: This is the first study to demonstrate that flaxseed can reduce blood pressure. In an earlier study, flaxseed oil had no effect on blood pressure in a group of normotensive individuals. The blood–pressure lowering effect of flaxseed might be due to lignans, which are present in high concentrations in the non-oil portion of the seed. A lignan present in sesame seeds has been reported to prevent the development of experimentally induced hypertension in rats.

Rodriguez-Leyva D et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension*. 2013;62:1081–1089.

Coenzyme Q10 for Statin-Induced Myopathy

Sixty patients (mean age, 58 years) with statin-induced myopathy (muscle pain, weakness, tiredness, or cramps) were randomly assigned to receive, in double-blind fashion, 200 mg per day of coenzyme Q10 (CoQ10), 200 μg per day of selenium, both treatments, or placebo for 3 months. In the groups receiving CoQ10 (n = 34), compared with baseline, mean intensity of muscle pain decreased by 52%, muscle weakness decreased by 60%, muscle cramps decreased by 65%, and tiredness decreased by 82% (all $p < 0.01$ compared with baseline and compared with the change in the groups not receiving CoQ10). No significant changes were seen in the selenium and placebo groups.

Comment: Statin drugs inhibit an enzyme that plays a role in the biosynthesis of CoQ10. Because CoQ10 deficiency can cause various muscle symptoms, it has been suggested that statin-induced myopathy is due in part to CoQ10 deficiency. Several previous trials have investigated whether CoQ10 supplementation can ameliorate statin-induced myopathy, and the results have been conflicting. It is not clear why CoQ10 was beneficial in some studies but ineffective in others. However, CoQ10 is safe (albeit somewhat expensive), so it is reasonable to recommend it for the prevention and treatment of statin side effects.

Fedacko J et al. Coenzyme Q10 and selenium in statin-associated myopathy treatment. *Can J Physiol Pharmacol*. 2013;91:165–170.

Does Eating Breakfast and Not Eating Late at Night Prevent Heart Disease?

The association between eating patterns and coronary heart disease (CHD) was assessed prospectively in 1992 in 26,902 American men (aged 45–82 years) participating in the Health Professionals Follow-up Study who were free of CHD and cancer at baseline. During 16 years of follow-up, 1527 cases of CHD were diagnosed. After adjustment for potential confounding variables, men who skipped breakfast had a 27% higher risk of CHD compared with men who did not (relative risk [RR] = 1.27; 95% confidence interval [CI], 1.06–1.53). Compared with men who did not eat late at night, those who ate late at night had a 55% higher CHD risk (RR = 1.55; 95% CI, 1.05–2.29). These associations were mediated by body mass index, hypertension, hypercholesterolemia, and diabetes.

Comment: Previous observational studies have found that eating breakfast is associated with lower total daily

caloric intake, lower total- and HDL-cholesterol levels, and improved insulin sensitivity. In addition, a recent randomized trial found that restricting nighttime energy intake resulted in a decrease in total daily energy intake and a decrease in body weight. In the present study, eating breakfast and not eating late at night were associated with lower CHD risk. Other benefits attributed to eating breakfast include minimizing impulsive snacking and reducing the risk of gallstone formation.

Cahill LE et al. Prospective study of breakfast eating and incident coronary heart disease in a cohort of male US health professionals. *Circulation*. 2013;128:337–343.

Double Standard in Media Reporting of Nutrition Research

The association between use of glucosamine and chondroitin supplements and mortality was examined in a prospective cohort study of 77,510 individuals (aged 50–76 years) living in Washington State. During an average follow-up period of approximately 7 years, after adjustment for potential confounding variables, all-cause mortality was significantly lower by 18% in individuals who used glucosamine (with or without chondroitin) than in those who did not use glucosamine. Use of glucosamine was associated with a significant 13% decrease in risk of death from cancer and a significant 41% decrease in risk of death from respiratory disease.

Comment: Observational studies such as this one do not prove causation, so it is not possible to determine from the data whether taking glucosamine actually decreases mortality. Consequently, this study is not newsworthy and, appropriately, it received little or no coverage in the media. Contrast that with the results of another observational study published in 2011, which found that the mortality rate was significantly higher by 6% in people who took multivitamins than in people who did not take multivitamins. That study was as weak as, or weaker than, the current study regarding glucosamine. Nevertheless, the press was all over the earlier study, with headlines proclaiming that vitamins can kill you. The differential reporting of these studies suggests a bias against nutritional supplements. Interestingly, in 2013, a meta-analysis of 21 randomized controlled trials found that the use of a daily multivitamin-multimineral supplement nonsignificantly decreased mortality by 2%, compared with a placebo (Macpherson H et al. Multivitamin-multimineral supplementation and mortality: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2013;97:437–444). Even though randomized controlled trials are far more reliable than observational studies, that study also received little or no press coverage.

Bell GA et al. Use of glucosamine and chondroitin in relation to mortality. *Eur J Epidemiol*. 2012;27:593–603.

N-Acetylcysteine for Endometriosis

Ninety-two infertile Italian women with ovarian endometriosis (large endometriomas, with a mean diameter of at least 30 mm) documented by ultrasound, who were scheduled to undergo laparoscopy 3 months later, were offered treatment with N-acetylcysteine (NAC) at a dosage of 600 mg 3 times per day for 3 consecutive days each week for 3 months. Those who accepted the treatment (n = 47, 73 endometriomas) were included in the NAC group, and those who chose not to try the treatment (n = 45, 72 endometriomas) were considered controls. After 3 months, the mean cyst diameter decreased by 1.5 mm in the NAC group and increased by 6.6 mm in the control group ($p = 0.001$ for the difference in the change between groups). The proportion of cysts that decreased in size was significantly greater in the NAC group than in the control group (62% vs. 28%; $p < 0.001$). Twenty-four patients in the NAC group cancelled the scheduled laparoscopy because of a decrease in cyst size (n = 14), disappearance of cysts (n = 4), or pain reduction (n = 21). Only 1 patient in the control group cancelled surgery. According to the authors, these results are better than those achieved with hormonal treatments. Eight pregnancies occurred in the NAC group and 6 in the control group. NAC was well tolerated.

Comment: Ovarian endometriomas are cysts of the ovary caused by endometriosis. They are associated with infertility. NAC has been shown to reduce the size of endometriomas in mice. The results of the present study suggest that NAC is also beneficial for women with ovarian endometriosis. The mechanism of action is not known.

Porpora MG et al. A promise in the treatment of endometriosis: an observational cohort study on ovarian endometrioma reduction by N-acetylcysteine. *Evid Based Complement Alternat Med*. 2013;2013:240702.

Gaby's Literature Review

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Thyroid Hormone Replacement Therapy: The Downside of Using Only Levothyroxine

One hundred thirty-five euthyroid patients who underwent total thyroidectomy for papillary thyroid carcinoma were studied. Thyroid function tests were performed preoperatively and at 2 time points postoperatively (usually at 6 and 12 months) while they were receiving stable doses of levothyroxine (T4). Serum TSH ($p < 0.001$) and free-T3 levels ($p < 0.03$) were significantly lower, and free-T4 levels were significantly higher ($p < 0.001$) postoperatively than preoperatively. The patients were divided into 4 groups according to their postoperative TSH level: strongly suppressed (less than $^1/_{10}$ of the lower limit of normal), moderately suppressed (between $^1/_{10}$ of the lower limit and the lower limit), normal range, and above the normal range. Patients with strongly suppressed TSH levels had serum free-T3 levels significantly higher than the preoperative levels ($p < 0.001$). Patients with moderately suppressed TSH levels had free-T3 levels equivalent to the preoperative levels. Patients with normal TSH levels had significantly lower free-T3 levels than the preoperative levels ($p < 0.001$).

Comment: The thyroid gland normally secretes both T3 (the biologically active form of the hormone) and T4. Conventional wisdom is that, for patients who need thyroid hormone replacement therapy, it is sufficient to administer T4 by itself, even though such treatment is not identical to what the normal thyroid gland secretes. Human enzymes (deiodinases) are capable of converting T4 to T3, and it is often assumed that hypothyroid individuals, when given an exogenous supply of T4, produce the exact amount of T3 they need. It is further assumed that monitoring the TSH level provides an accurate assessment of whether patients are receiving an appropriate doses of T4. However, many doctors have observed that some patients do not feel well until their T4 dosage is increased to a level that suppresses the TSH.

The results of the present study support those clinical observations, because patients whose thyroid glands had been removed required TSH-suppressive doses of T4 in order to achieve their preoperative free-T3 levels. Previous research in animals found that the disconnect between TSH and T3 levels occurs when T4 is given by itself, but not when a combination of T4 and T3 is administered.

There are two take-home points from this research. First, the combination of T4 and T3 may be preferable to T4 alone for people who require hormone replacement therapy. Second, when T4 is given by itself, measuring both TSH and free-T3 levels may give a more reliable indicator of dosage requirements than would measuring only TSH.

Ito M et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. *Eur J Endocrinol.* 2012;167:373–378.

Do Acid-Suppressing Drugs Cause Food Allergy?

Using a large national insurance database in the US, 4724 children (mean age, 3.1 years) diagnosed with gastroesophageal reflux disease (GERD) who were treated with gastric acid suppressive (GAS) medications were identified. These children were matched with 4724 children with GERD who were not treated with GAS medications and 4724 children without GERD and not treated with GAS medications (controls). The groups were matched for age, gender, and risk factors for atopic disease. During a 12-month follow-up period, food allergies developed in 1.61% of the children treated with GAS medications, 0.87% of the children with GERD who were not treated with GAS medications, and 0.36% of the controls. The incidence of food allergy was 68% higher among the GERD cohort treated with GAS medications than among the GERD cohort not treated with GAS medications (hazard ratio = 1.68; 95% confidence interval, 1.15–2.46). Children with GERD who were not treated with GAS medications were significantly more likely to develop food allergies than were controls.

Comment: GERD is a common problem in children. Treatment with medications that suppress gastric acid secretion may lead to impaired protein digestion, resulting in the absorption of allergenic protein fragments and sensitization of the immune system. GERD in children appears to be caused at least in part by allergies to milk and other foods, and the use of GAS medication to reduce symptoms may, ironically, exacerbate allergies.

Trikha A et al. Development of food allergies in patients with gastroesophageal reflux disease treated with gastric acid suppressive medications. *Pediatr Allergy Immunol.* 2013;24:582–588.

Nightshade-Free Diet for Itchy Scars

Chronic pruritus occurs in most scars that form after serious burns, and in some surgical scars and keloids. Some patients have observed that intake of certain foods exacerbates their postburn pruritus. Based on patients' reports, the authors of this study advised a woman who had had postburn pruritus for 6 months to avoid nightshade foods (i.e., potato, tomato, eggplant, and peppers). The pruritus disappeared completely within 1 week, and the woman remained symptom free except on 1 occasion when she ingested tomato soup. Subsequently, the authors recommended a 1-week trial of a nightshade-free diet to 15 patients with pruritus of postburn scars (n = 7), surgical scars (n = 6), or keloids (n = 2) that had been refractory to antihistamine treatment. Three patients did not follow the recommendation and experienced no improvement. Among the 6 patients with postburn scars who followed the recommendation, 4 experienced 100% relief and the other 2 experienced 80% to 90% relief. Among the 5 patients with surgical scars who followed the recommendation, 3 experienced 100% relief, 1 experienced 50% relief, and 1 had no improvement. The 1 patient with keloids who followed the recommendation reported 95% improvement.

Comment: Nightshades contain solanine alkaloids, which have been found anecdotally to be a triggering factor for joint pain in some people with osteoarthritis, as well as a cause of various other symptoms in susceptible individuals. The mechanism by which these alkaloids might cause pruritus in scars is not known.

Alonso PE et al. Solanaceae-free diet for scar pruritus. *Burns.* 2013;39:534–535.

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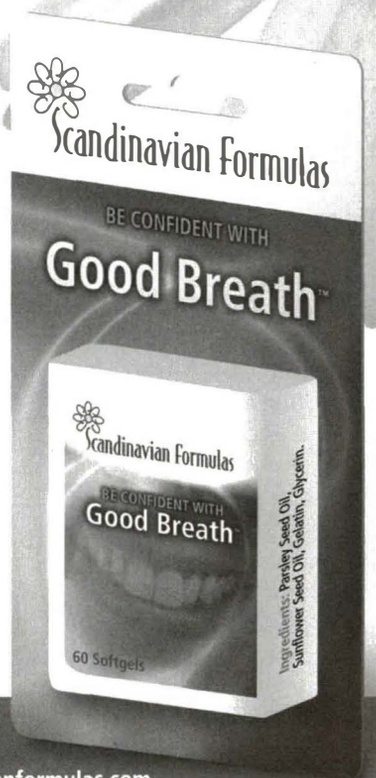

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Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Change of Heart: Reducing Cardiovascular Disease Risk at the Flip of a Coin

Introduction

Solid scientific evidence exists for using nutrition in the treatment of cardiovascular disease, with many resources available to help streamline patient education and not prolong office visits (see text box). Yet, uptake of nutritional interventions still remains low. The juggernaut is patient receptiveness and willingness or ability to make the daily changes in food selection towards a plant-based diet.

This *Townsend Letter* themed on cardiovascular health presents a novel teaching "pocket" guide: Flipping a US quarter to its reverse side can engage the adult learner (i.e., your patient) in cardiovascular disease prevention.

Health professionals attempt to teach adult learners what they think they already know but don't. In fact, "doctor" means "teacher." The word origin is more than semantics because health professionals must overcome what pedagogues consider to be among the toughest challenges: communicating healing messages that require penetrating formidable barricades of denial and fear. This column offers a way to engage the patient in a conversation on dietary change which is not uncomfortably personal, but poignant.

The following four game-show style questions each pertain to the reverse side of a US quarter. They equip practitioners to prescribe lifestyle changes critical to cardiovascular disease reduction, in new ways that patients haven't heard before.

1. **Question**: What is featured on the reverse of the 1999 Georgia state US quarter?

   Answer: The peach.

According to food experts, no perfect Georgia peach should ever find itself in a jam. The demand for peaches and the other fresh produce from this originally agricultural state should be so high that there are literally none left over. If all Americans consumed the recommended 5 to 7 daily servings of fruits or vegetables, only 50% to 80% of the demand could be supplied initially. Eventually food markets could readjust; however, it takes many years for those peach trees to bear fruit. Now, if only fewer Georgia streets were bearing the name "peach," perhaps its city highways would have fewer jams.

Encourage your patients to contribute to the demand for fresh fruits and vegetables, in such a way that the supply side notices it.

2. **Question:** What food source used by South Carolina patriots is recognized on its flag and the US quarter commemorating the state?

   Answer: The sabal palmetto, also called the cabbage palm.

Resources on Nutrition and Cardiovascular Disease Reduction

Nutrition reroutes and revises metabolic pathways toward cardiovascular health. The scientific evidence for nutrition in heart disease is among the most compelling. Many practical clinical protocols are found in *Advancing Medicine with Food and Nutrients* (Kohlstadt I, ed. CRC Press; 2013). Beyond dyslipidemia and hypertension, diet and nutrient interventions also influence blood viscosity and recurrence of cardiac arrhythmias.

Nutrition for the treatment of cardiovascular disease is also presented in many consumer health books. Two books that I have recently read and reviewed are *The Adaptation Diet*, by Charles A. Moss, MD, and *Eat Well, Age Better*, by Aileen Burford-Mason. Books such as these can be effective prescriptions and impose little on clinic time.

According to the history books, in 1778 heart of palm saved the heart of America. South Carolina patriots fended off the British soldiers from a quickly assembled palmetto log fort. At first read, this may sound completely unrelated to nutrition. But look again. Food supplies had been cut off to the colonies' southern reaches. Hungry patriots were wading in swampland with only a musket and axe. The food that sustained them was the palmetto, plentiful in the region. They ate the heart of palm, which has a taste resembling artichoke. Since the Northern European descendants probably weren't familiar with artichoke, they found it comparable in taste and layered appearance to cabbage. Today heart of palm is seldom eaten because the agriculture is not sustainable. Young trees must be felled, and heart of palm is the reason that the palmetto logs were on hand for the patriots' victory fort.

Today many palm products protect the hearts of Americans. Encourage your patients to remember the cabbage-palm quarter when thinking about what they can eat that's heart healthy.

3. **Question**: What food with cardiovascular health benefits is featured on the 2008 Arizona US quarter?

   Answer: Cactus pears.

Medical traditions of the people indigenous to Arizona incorporated cactus fruit into their healing remedies. When looking at the saguaro cactus towering 70 feet with upright appendages, such as the saguaro featured on the coin, it's easy to infer that the fruit of this plant was revered for improving male sexual vitality. Modern science now provides evidence that this longstanding belief is not a fallacy (phallus-y). Cactus fruit is rich in antioxidants, produced by prickly pear and saguaro in order to withstand the intense desert heat and ultraviolet light. Incorporating these antioxidant phytonutrients into the human diet supports vasculature throughout the human body. Now if there were only an easier way to harvest the saguaro cactus fruit.

Encourage patients to connect with ethnic foods and learn the food ways of their region. Some of the most heart-healthy foods are right in our reach.

4. **Question**: What tree is featured on the first coin ever minted by the American colonies and more recently on the 2013 US quarter minted to feature Great Basin National Park?

   Answer: Pine.

The 2013 US quarter from the America the Beautiful series depicts Nevada's Great Basin with a windswept landscape and bristlecone pine tree. The pine tree is also featured in the first coin ever minted by any of the colonies – the Massachusetts Bay Colony Pine Tree Shilling was minted from 1652 to 1683.

The shilling was foretelling. Pine was valued for its wood and also as a food source. Pine needles were used to make tea, often by placing needles in a jar of water left to steep in the sun. No heating is needed for the vitamin C and other nutrients to leach into the water. Sailors prepared pine tea to fend off scurvy, a claim that could not be made by British tea. In other words, the health of the Massachusetts Bay Colony would have benefited from dumping British tea into Boston Harbor long before 1773!

Pine-needle tea doesn't have to be just for history books. It should also be in medical books. It can be an entry into learning about edible wild plants or simply taking nature walks. In addition to adding healthful foods, nature walks combine exercise, being outside, and exposure to phytonutrients.

Summary

As health-care practitioners, we can help patients "change" their health, with the flip of a coin. Reminders can include poster-sized images in a waiting room, an introduction slide to a group medical therapy talk, or a casual story of nutrition and American history during a relaxed patient procedure. When patients find the coin in their handful of change at the grocery store, their purchases might look a bit more plant-based. And that's the start of a change in heart.

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Images are provided from the US Mint (usmint.gov).

Protocol Controversies for Treating Cardiovascular Disease with EDTA Chelation Therapy

by L. Terry Chappell, MD, and Jeanne A. Drisko, MD, CNS

Introduction

The Trial to Assess Chelation Therapy (TACT) is the only large, randomized clinical trial to provide statistically significant evidence that EDTA chelation therapy with high-dose multivitamins can reduce future cardiac events in patients with known cardiovascular disease.[1,2] TACT utilized the published protocol that is used by organizations such as the American College for Advancement in Medicine (ACAM), the International College of Integrative Medicine (ICIM), the American Board of Clinical Metal Toxicology (ABCT), and the International Board of Clinical Metal Toxicology (IBCMT), all of which teach physicians how to administer the therapy and/or test them to provide certification.[3]

TACT used an intravenous dose of 3 g of disodium EDTA with magnesium, adjusted downward if kidney function was compromised, 7 g of vitamin C, 500 cc of sterile water, and several minor additives, all infused over a minimum of 3 hours.[1,2] (See Table 1.) The published protocol is more flexible, allowing for 1.5 g to 3 g of disodium magnesium EDTA over no more than 1 g per hour and varying amounts of vitamin C, as long as the osmolality of the treatment solution is not hypotonic and not so hypertonic as to cause problems. Calcium EDTA has also been used in various forms with claims of effectiveness for vascular disease. The use of calcium EDTA, especially in the oral form, to treat cardiovascular disease has been criticized by the teaching organizations mentioned above. Concerns have also been raised about high doses of vitamin C, which becomes a prooxidant instead of an antioxidant at certain levels.[4]

The purpose of this article is to discuss the rationale, evidence, and experience of physicians who are acknowledged experts in the use of EDTA for treating cardiovascular disease. We hope to clarify whether calcium EDTA should be used to treat vascular disease and how much EDTA and vitamin C are effective and safe to use.

The Published Protocol

TACT used the 3 g basic dose of disodium EDTA with magnesium to treat patients who had a history of documented myocardial infarction. The basic protocol for TACT is shown in Table 1. The 3 g dose for disodium EDTA has been taught for years, and many doctors who provide intravenous chelation therapy use it routinely. However, there is evidence that a lesser dose might be just as effective.[6–9] As a result, a substantial number of treating physicians use the lesser dose, based on these reports. Obviously, a lesser treatment time is more convenient for patients. Neither dose puts the kidneys at risk as long as the required rate of administration is followed. For patients with congestive heart failure, a lesser fluid volume for the treatment might be advantageous.

Table 1: Infusate Used in TACT

Component	Amount
Na2EDTA	3 g
Magnesium chloride	2 g
Procaine HCl	100 mg
Heparin	2500 units
Ascorbate (vitamin C)	7 g
KCl	2 mEq
Na bicarbonate	840 mg
Pantothenic acid	250 mg
Thiamine	100 mg
Pyridoxine	100 mg
Sterile water	To 500 mL

The mixture of components given in TACT was based on committee consensus bewteen the TACT investigators and representatives of the chelating community. The agreed-upon solution was selected as the representative mixture that had been in use. The amount of EDTA administered to the trial participants was tailored to the individual renal function based on the Cockgroft-Gault equation.[1–3]

Chappell and Stahl performed a meta-analysis of studies showing objective improvement for patients with cardiovascular disease treated with intravenous EDTA chelation therapy.[5] Nineteen published studies involving 22,765 patients met the inclusion criteria. All of these studies used the 3 g dose of EDTA with one exception. Olszewer and Carter treated 2482 patients with the 1.5 g dose, and 2379 improved.[6] In the meta-analysis, 87% of patients improved, and there was a correlation coefficient of 0.88 between improvement in vascular function and treatment with EDTA. Patients of the physician who used the 1.5 g dose did as well as those from the other sites combined.

Chappell and associates did a follow-up meta-analysis of 32 unpublished reports on 1241 patients.[7] 1086 or 88% showed measurable improvement. 778 patients were treated with the 1.5 g bottle. A comparison of the 1.5 g and 3 g doses in this study showed almost identical results.

Born and Geurkink published a retrospective, randomized study comparing patients with peripheral artery disease treated with the 3 g dose of EDTA to those treated with the 1.5 g dose.[8] 20 treatments were given to 15 patients in each group. Those treated with the lower dose improved using Doppler ultrasound by an average of 123%. The patients in the 3 g group improved by an average of 70%. The results were statistically significant. One patient treated with 1.5 g improved 715%. That patient was omitted from the study as an outlier.

Chappell and associates compared 220 vascular patients treated with a basic course and maintenance chelation with matched controls from the literature.[9] An average of 58 treatments were given. Subsequent cardiac events were much less in the EDTA-treated group. The patients treated with the 1.5 g dose had virtually the same results as those with the 3 g dose.

An in vitro study published in *Surgery* in 1962 showed the mobilization of calcium from atherosclerotic plaque with EDTA in the laboratory.[10] The results demonstrated that the longer the tissue is exposed to EDTA, the more calcium was removed. To our knowledge, this finding has not been confirmed in vivo.

Blaurock-Busch observes that the German Chelation Society approves both a 2 g and 3 g dose.[11] Gordon wrote the first American Academy of Medical Preventics (AAMP) chelation protocol in 1972, based on the work of such pioneers as Clark and Lamar. It was not published, but it was used in coursework for many years. He listed the EDTA dose of 50 mg/kg. Cranton's 1989 textbook refers to a maximum of 3 g dose, except for large patients who could receive up to 5 g at 50 mg/kg. The textbook was updated in 2001.[12] Rozema's protocol for EDTA lists both a 3 g and 1.5 g dose, as does van der Schaar's 2012 textbook.[3,13] The latter has a maximum of 4 g for large patients. All of these protocols insist on an infusion rate of disodium EDTA not faster than 1 g per hour to avoid overloading the kidneys.

Because of TACT, the best evidence for treatment of vascular disease with intravenous disodium EDTA lies with the 3 g dose. However, the published studies cited above that compare the 3 g dose with the 1.5 g dose show the latter to be as effective. As noted, one study showed the 1.5 g dose to be more effective for peripheral vascular disease. Future large clinical trials will be necessary to determine the lowest amount of EDTA that can produce the best outcome in cardiovascular disease.

Mechanisms of action for EDTA

Proposed mechanisms of action for EDTA chelation therapy have been documented, but no consensus exists as to which mechanism(s) are most important to treat vascular disease.[14] It is well known that both disodium EDTA and calcium EDTA can remove heavy metals. Such metals as lead, cadmium, and mercury increase the risk of vascular diseases by increasing free radical activity.[15] Reduction of free radicals by EDTA infusions reduces inflammation, which might lesson the likelihood of the rupture of unstable plaques.[16] The clot that occurs as a result of this rupture is the accepted mechanism for most myocardial infarctions and strokes. A small study by Chappell and Angus showed a reduction of brachial artery stiffness with chelation.[17] Iron deposits have been found in macrophage foam cells, which further increase free radicals and inflammation. Excessive copper also increases free-radical activity. EDTA chelates both iron and copper.[18]

Lowering blood calcium levels with intravenous boluses of disodium EDTA can inhibit platelet aggregation for weeks at a time.[19] Intravenous EDTA has been proposed as a safer substitute for clopidogrel to prevent clotting after inserting drug-eluting stents.[20] The anticlotting effect is likely to be an important mechanism for chelation's cardiovascular benefits. Selye demonstrated harmful deposition of calcium in soft tissue when a sensitized individual is exposed to a new challenge after a suitable interval.[21] The drop in serum calcium that occurs almost immediately upon IV infusion of disodium EDTA stimulates parathyroid activity. Parathormone mobilizes calcium from soft tissue deposits, but the effect is irregular. Although there are case reports that plaque can be reduced with disodium chelation, studies have not shown a predictable improvement in lumen size for arteries blocked with plaque. It is possible that the calcium reduction cascade stabilizes vulnerable plaques, but this also has not been proved.[22,23]

High doses of magnesium are put into the intravenous treatment solution, which prevents adverse effects from the brief drop in calcium levels. Improved levels of intracellular magnesium might reduce irritable foci that cause arrhythmias and lower blood pressure. To prevent progressive calcium depletion, it is important that IV infusions of disodium EDTA be given no more often than 2 to 3 days per week, with at least 24 hours between treatments. With 60 years of use of intravenous disodium EDTA for vascular disease, no fatalities have been attributed to EDTA when the protocol has been followed. However, there have been isolated fatalities when disodium EDTA was administered by rapid IV push.

Nitric oxide (NO) is an important signaling molecule that is antiatherosclerotic. NO production declines with age and is worse with a high-fat diet. Lead inhibits NO

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formation. EDTA not only removes lead but also independently increases NO production.[24] This might be an important mechanism for improved circulation for both disodium EDTA and calcium EDTA.

Vitamin K2 also might help remove metastatic calcium from arterial walls. It has been suggested as an oral supplement to augment the decalcifying effect of disodium EDTA.[25] However, vitamin K2 is not currently included in the chelation therapy protocol.

Calcium EDTA

Intravenous calcium EDTA is approved for removing lead and is used to treat accumulations of other toxic metals. Since there is no reduction of serum calcium as is seen with disodium EDTA, certain mechanisms that are proposed for treating vascular problems do not apply. Specifically, metastatic calcium is not mobilized and platelets are not inhibited.

Oral, sublingual, transdermal, and rectal EDTA all consist of calcium EDTA. Oral EDTA is only about 5% absorbed. Rectal EDTA might be absorbed as much as 35% to 37%.[26] Intravenous calcium EDTA is used widely as a challenge test and a treatment for toxic metals. It was used in a small study by Lin that showed that nondiabetic patients with moderate kidney disease might progress less rapidly with EDTA treatment than without.[27] Chen and associates showed that diabetic nephropathy in the presence of high lead levels progressed at a slower rate than controls when their lead levels were reduced and kept under control with 1 g calcium EDTA treatments IV.[28] High levels of lead have been shown to be associated with lower blood pressure and an increased risk of vascular disease.[29] Reducing the lead burden might result in improved blood pressure and better circulation to the kidneys. However, without a drop in serum calcium, decalcification of the arterial wall is highly unlikely. The many published studies showing improvement in vascular disease, including TACT, all have used disodium EDTA with magnesium.

Gordon has proposed that calcium EDTA combined with lecithin and other nutrients improves blood viscosity, and he cites the work of Lowe and others.[30] One might expect this to be the case since lavender-top tubes with EDTA are used to anticoagulate blood drawn from patients for testing. However, the EDTA used for that purpose is potassium EDTA (K2EDTA), not calcium EDTA. We were unable to find evidence that calcium EDTA reduces platelet activity directly. One mechanism for inhibition of platelet aggregation is a depletion of calcium ions. However, another probable mechanism that applies to calcium EDTA is its stimulation of the production of NO. Several oral nutrients that can lesson platelet aggregation, such as vitamin E and gingko, can be given orally along with calcium EDTA.

Cranton points out on his website a potential danger of oral chelation.[31] Some toxic metals that are ingested might not be absorbed into the body if calcium EDTA is present, but many more essential minerals will also not be absorbed. Depletion of zinc, chromium, copper, manganese, and other minerals can reduce antioxidant defenses and endocrine function. Cranton stresses the importance of the rapid decrease in both toxic metals and calcium with disodium EDTA. This occurs extracellularly, since EDTA does not enter the cells. A reequilibration results so that calcium is mobilized as described above and toxic metals are brought out of storage in the bone, brain, and fat cells.

Calcium EDTA is widely sold and advertised as an ingredient in various nutritional supplements. Claims of effectiveness for calcium EDTA in treating vascular disease are often made based on research that was done for intravenous disodium EDTA. Calcium EDTA and disodium EDTA are two separate compounds that act on calcium differently in the body. Although useful mechanisms of action might apply for calcium EDTA, we did not find any clinical trials that support the use of calcium EDTA for treating vascular problems.

Van der Schaar's textbook describes many toxic metals and chelating agents.[13] DMSA, DMPS, and the two forms of EDTA are commonly used in clinical practice at this time. DMSA is available orally and is used to chelate lead and mercury in adults and children. DMPS is a compounded substance for oral or IV use, mostly for lead and mercury, but it is *not an FDA-approved medication.* DFO is sometimes used parentally for iron overload, but serial phlebotomies are generally more effective. D-penicillamine can be helpful as a challenge test and occasional treatment. These medications can be used in combination if the prescribing physician is experienced. The two forms of EDTA are broader chelators and are especially effective for lead. EDTA has perhaps the weakest affinity for mercury. If mercury is elevated with a challenge test, it might be prudent to treat with DMSA or DMPS before prescribing intravenous EDTA. Maintaining good levels of beneficial minerals is important no matter what chelation agent(s) is/are prescribed. Treatment with DMSA or DMPS reduces free radical activity by binding and excreting heavy metals, which might be beneficial. However, we did not find any clinical trials that have studied either one as a treatment or preventative for vascular disease.

Vitamin C

As with any medical practice, whether conventional or alternative, different approaches and individualized styles of practice evolve. Some of the differences in approaches relate to experience and some are based on growing evidence from the scientific literature. And

so it is with EDTA chelation therapy with certain groups giving differing amounts of EDTA over varying times and by different routes of administration, while others advocate using different formulations and combinations of additives in the mix. One proposed change has been the recent suggestion that vitamin C or ascorbic acid be removed from EDTA chelation therapy because of its known action as a prooxidant in the extracellular space in living systems.[4,32-34]

Seminal findings regarding the unexpected prooxidant action of intravenous vitamin C were discovered in the National Institutes of Health (NIH) lab of Mark Levine, MD, along with his colleagues, Qi Chen, PhD, and others.[33,34] Levine and colleagues clearly defined that oral vitamin C was a vitamin with tight physiologic control and antioxidant properties, while intravenous vitamin C administration bypassed tight control and through Fenton chemistry became prooxidative in the extracellular space.[35-37] In people with normal G6PD status, the prooxidative nature of vitamin C *does not occur* in the vascular space.[34]

It is interesting that another well-known antioxidant, glutathione, does not behave like vitamin C when injected in high doses.[38] Glutathione maintains its antioxidant properties even when injected at increasing concentrations and has led to the recommendation against adding IV vitamin C and IV glutathione together at the same setting.[38] To date, other antioxidants such as alpha lipoic acid have not been evaluated in this manner to determine if they might exhibit a dual nature like vitamin C.

The prooxidative nature of intravenous vitamin C has led some to postulate that adding vitamin C to EDTA chelation therapy might have a deleterious effect on patients with already high oxidative burden, as seen in diabetes.[4,32] The hypothesis is that patients with oxidative disease processes may not be able to tolerate the additional oxidative burst that briefly occurs after intravenous vitamin C. Roussel and colleagues conducted a small uncontrolled trial in 6 adults where EDTA chelation therapy was administered according to standard protocol except for elimination of the vitamin C from the infusate.[4] In the reported trial, markers for oxidative damage were evaluated in the absence of added vitamin C and were found not to be present. The group concluded that EDTA chelation therapy without added vitamin C decreases oxidative stress. But as Roussel and colleagues clearly stated, the small trial was not designed to test

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the curative effects of the chelation therapy. They acknowledged they were focusing solely on antioxidative effects.

The Roussel trial is in contrast to TACT, wherein 1708 participants with known cardiovascular disease were enrolled.[2] The sample size was chosen so that the effect of EDTA chelation therapy on cardiovascular outcomes could be evaluated. The standard accepted protocol was chosen and this included 7 g of vitamin C injected at each infusion.[1] An unexpected and remarkable finding at the conclusion of TACT was the marked reduction in cardiovascular events in diabetic participants.[2] This has prompted the NIH to ask researchers to focus on the positive effects in the standard EDTA infusate that may have promoted such beneficial outcomes.[39] However, the belief that intravenous vitamin C is a harmful prooxidant has led other experienced practitioners of chelation therapy to abandon the addition of vitamin C to the mix.[32] The trial findings with the small sample size and the concerns raised by Roussel and colleagues are contradicted by the positive outcomes of TACT.

What then is the effect that vitamin C plays in the chelation infusate? Is it related to the prooxidative burst? Is it related to other as yet undescribed effects, apart from Fenton chemistry? It is advisable to remember that in the vascular space, when there is normal G6PD status, there are no significant detectable levels of hydrogen peroxide and no detectable prooxidant effect.[33,34,40] Any hydrogen peroxide that might be formed after infusion of vitamin C is quickly and effectively quenched in the vascular space, unlike what occurs in the extracellular space. Is it possible that vitamin C at increased concentrations has an effect on the endothelium? Or on the function of blood elements such as the red blood cells that are so critical for oxygen mobilization? Unpublished research carried out by the Levine team points to this possibility.

The epidemiology literature shows that vitamin C is critical for improvement of HbA1c and avoiding untoward effects in diabetics.[41] However, it can easily be argued that this is a vitamin effect, not a pharmacologic effect. In the tobacco literature it has been shown that the prolonged and destructive exposure to tobacco smoke markedly reduces available vitamin C levels in vivo that are only replenished effectively with intravenous infusion.[42–46] Functional effects on the microvascular bed can be reversed with IV vitamin C.[43,45] It can be argued that tobacco smoking is a model for highly oxidative chronic diseases such as diabetes. Benefits of infused vitamin C could have positive effects on microvasculature function. This would certainly be a good model for future research.

Other nonvascular effects of IV vitamin C also come into play, such as the effects of ascorbate in steroidogenesis, vascular tone, adrenal gland function during stress, and general well-being.[47–50] Taking the narrow view that vitamin C acts as only a prooxidant or an antioxidant may result in the risk of excluding vitamin C with its various positive functions, both known and as yet unknown, in the beneficial treatment of cardiovascular disease with EDTA chelation therapy.

Conclusions

Scientific evidence, especially with TACT, supports intravenous disodium EDTA with magnesium, along with oral multivitamins, to treat vascular disease. Disodium EDTA can only be given by slow intravenous drip, at a rate no faster than 1 g per hour. Under no circumstances can this preparation be given by intravenous push because of its effect to rapidly lower serum calcium. Evidence supports treatment doses of 1.5 or 3.0 g of disodium EDTA. The dose should be reduced if kidney function is impaired. Kidney function should be monitored during the course of treatment. Treatments should be limited to no more than 2 or 3 days per week with at least 24 hours between treatments. 20 to 30 treatments are needed to complete a basic course of treatment for vascular disease.[3] More treatments may be required in difficult cases. Most experts recommend monthly maintenance after the basic course is completed. If the published protocol is followed, safety is not an issue.[2] Disodium EDTA with magnesium effectively removes heavy metals from the body. Other likely mechanisms of action include reduced platelet aggregation, mobilization of metastatic calcium by parathormone, increased NO production, and antioxidant activity.

Calcium EDTA can be given intravenously or by other routes of administration to remove toxic metals. Oral absorption is only 5% and rectal absorption might be as high as 35% to 37%. Calcium EDTA does not have all the mechanisms of action that disodium EDTA does to reduce or prevent vascular disease. However, calcium EDTA with multivitamins increases NO production and decreases free radical activity. Moderately impaired kidney function might improve with IV calcium EDTA. Clinical trials have not been done to support calcium EDTA as a treatment for vascular disease at this time. Calcium EDTA should not be given on a continuing basis without being careful to avoid depletion of essential mineral nutrients. Optimal mineral balance might be difficult to accomplish with oral preparations given on a daily basis.

At this juncture because of the positive TACT outcomes, vitamin C should not be excluded from or reduced in the infusate. The hypothesis that IV vitamin C results in a significant deleterious oxidative burst has not been borne out and as part of the total chelation component seems to provide an additional benefit in patients with diabetes and cardiovascular disease.

As shown in other conditions with high oxidative environments, IV vitamin C can provide protection and vascular stability. Exciting research opportunities lie ahead in parsing out the effect of the various chelation components in treating cardiovascular disease.

Comments from a Few Experts

Ralph Miranda: I suspect that the most consistently effective dose is the 3 grams of disodium-magnesium EDTA in the 500 ml bag/bottle infused over 3 hours. I believe that the attraction of metal ions and ligands causes enough of a shift in pools of metal ions, that previously inhibited enzymatic reactions are liberated from the effects of toxic metals and permitted to contribute to normal and desirable repair processes for which they are suited. Remove the poisons from the systems, and the systems work closer to their innate abilities, to clean up the damage inherent to everyday life.

Of course, some patients are too frail to withstand the higher dose or the greater fluid volumes, so the 1.5 g dose infused at the same rate over half the time or a bit longer suits them well. I'm convinced that the patients who get the "half dose" get far more than "half" the benefit. This dose also works well for patients who are not at liberty to spend as much time away from work, or in my office. Another reason to tread lightly would be patients on multiple pharmaceuticals or with multiple intertwined medical conditions

I will also use the calcium disodium EDTA, especially when the sole focus of treatment is removal of specific toxic metals. I am not a fan of the rapid infusion of this mixture, even though many chelating docs recommend the rapid push due to the absence of risk for hypercalcemia. I believe there is plenty of potential for disruption of physiologic levels of Zn, Mn, Cr, and other trace metals from too rapid an injection. Oral EDTA and rectal suppositories share the lack of significant absorption for purposes of CVD and reducing metals. These are the least effective choices, and I reserve them for those who cannot, for whatever reason, use the IV therapies.

Michael Schachter: I generally follow the ACAM protocol, using Cockgroft-Gault to calculate the proper dosage with a maximum of 3 grams of EDTA. My infusions are generally 3 hours. We have used catheters exclusively for many years to avoid butterflies' tendency to come out of the vein when the patient moves around. If my primary goal is removing lead or cadmium, I use calcium EDTA instead of disodium EDTA and usually run the infusion over 20 to 30 minutes.

Claus Hancke: Since 1987 I have been using the same protocol with great success and not one single fatality or serious side effect in nearly 100,000 infusions. Nothing is added that can be given as effectively orally. My carrier solution is 250 cc of isotonic glucose. This does not create problems with diabetic patients and avoids a saline load for those with heart failure. Magnesium and bicarbonate avoid infusional pain and tremor. I use 3 g of EDTA and have recently reduced from 5 g to 2 g of vitamin C. My infusions last 3 hours.

We EDTA doctors of the world have been using the EDTA chelation protocol mainly unchanged from 1987. Now, after 25 years, we have succeeded against our opponents and can show the TACT study with significant results. So I don't think it is *politically* wise to change the protocol right now. Let's make serious trials to see the efficacy of different infusion modalities, but never give up what we have established.

Ted Rozema: Hans Seyle comments in his book *Calciphylaxis* about how PTH is a direct producer of calcium deposition in arterial walls. My personal take on the deposition of calcium in arterial walls leading to atherosclerosis is that as we age, the fundus of the stomach does not produce the gastric acid needed to embed a marker on the calcium molecule so it can be seen by the gut villi cells and be invited into the bloodstream. This will cause not enough calcium to be absorbed to maintain the tightly controlled calcium balance in the bloodstream. Over time, there is a miniscule parathyroid hormone release to take calcium from the bone to make up the shortfall. This produces the sensitization to put some of the calcium into arterial walls. Over many years, the clinical picture of early death and other vascular conditions result.

The issue of using calcium EDTA (instead of magnesium disodium EDTA to reduce metastatic calcium and treat vascular disease) is embedded in the use of magnesium disodium EDTA. Once the latter molecule hits the bloodstream, the magnesium is dropped for chelation of calcium. The resulting decrease in free serum calcium is what triggers the parathyroid action (and the platelet effect). The resulting calcium disodium EDTA will then do all the toxic metal binding that calcium disodium EDTA does when given as a short IV infusion. ...

Joe Hickey: I believe that mercury is chelated with EDTA. The resulting mercury EDTA rapidly vaporizes from urine and thus is difficult to measure. If one believes that neither CaNa2 EDTA nor MgNa2 EDTA effectively chelates mercury, then one must account for mercury with DMSA or DMPS. If urine and fecal measurements are done, the largest amount of heavy metals removed is by far mercury with lead a distant second place. If only urine is collected, lead is usually the highest excretion with mercury second, in my patients. Therefore, I also use DMSA if tolerable with either form of EDTA to account for mercury. I will give 10 mg/kg of DMSA for three days, starting on the day of the IV with EDTA. DMSA is less likely to vaporize in the stool. ➤

When treating primarily for vascular disease, I use MgNa2 EDTA 1.5 g over 1.5 hours with the addition of the DMSA. I have found this regimen to be successful in patients who have had recurrent angina, post bypass, and stent closure. I am rarely able to talk patients into consistently sitting for the 3 g/3-hour infusion. I believe that there is probably an additional effect for the 3-hour infusion in cases of calcific valvular disease and scleroderma, because of the parathyroid effect, but I am not convinced that the 3 g dose is the sole treatment for vascular disease. In younger patients with fibromyalgia or neuropathy, I will usually use CaNa2 EDTA in combination with DMSA. If DSMA is not tolerated, I will alternate with DMPS.

John Trowbridge: What are we trying to accomplish with chelation treatments? If a patient is substantially "loaded" with toxic metals, treatment goals will be different than those for one with high-grade blockage disease in critical arteries. Patients suffering with crippling inflammatory and/or autoimmune diseases might require a another approach.

Injectable and oral medication alternatives to EDTA should be considered, depending on a variety of factors. However, 60 years of beneficial and safe reports regarding EDTA would argue for that to be the basic IV chelator. Others could be added in ways that maximize their safety considerations as well, such as oral DMPS, DMSA, and d-penicillamine, as well as IM DFO.

With different stability constants and side effects, using two or more chelating agents at the same time poses potential risks to the patient. The simplest way to avoid such unpredictable interactions is to administer one chelating drug at a time. In 1993 I developed the idea of administering different chelating drugs on an intermittent, pulsatile schedule. This protocol avoids the potential of interaction of two or more chelation drugs but still allows for exploiting the "preferences" of each drug for different toxic metals. Extra physiologic minerals would, of course, be needed to handle the additional chelator load.

To minimize side effects, I have patients take 1 250 mg tablet each evening during the week. For example, a patient might be advised to take d-pen 250 mg each bedtime on days 1–7 of the month, then DMSA 250 mg each bedtime on days 8–14, then d-pen again on days 15–21 and DMSA again on days 22–28, with a "break" until day 1 of the next month. I do not mix IV EDTA with DFO, nor do I give d-penicillamine or DMSA within 4 to 6 hours of EDTA IV.

With the changing urinary elements test reports, a patient might be told to take just d-pen or DMSA every day of the month. Now that oral DMPS is readily available, it might be inserted into the "weekly" protocol as well, especially when mercury levels are substantially elevated on the test report.

By 1997, I had confirmed that our reduction of toxic heavy metal body burden – as measured by the d-Pen challenge urinary elements test – was proceeding at a rate at least one-third faster than with IV EDTA alone.

Two serious mistakes that beginning doctors often make when giving chelation therapy are insufficient attention to mineral depletion and too rapid reduction of cardiovascular medications. Ample minerals must be supplied, either orally or IV, and gradual reductions of meds are required in order for the body to "relearn" more normal functions.

Conrad Maulfair: With calcium being an important factor in the aging process and in the atherosclerotic disease process, we want to have the maximum benefit from its removal that is possible. I personally am a strong advocate of the 3–4 hour chelation treatment simply based on clinical experience.

Patients suffering from end-stage chronic degenerative diseases are misled when they read or are told that oral application of chelating agents and in particular EDTA can be an alternative to a comprehensive chelation therapy program including the parenteral administration of EDTA. A patient having significant end-stage disease opting to take an oral chelation product because it is cheaper and does not require a personal commitment of time and involvement is most assuredly going to experience a poor outcome. A practitioner who encourages a patient with significant disease to think that using oral chelation is better than doing nothing is being as irresponsible as allowing a patient uncontested to continue to smoke one pack of cigarettes a day because it is better than the two packs a day that he/she had previously smoked.

Garry Gordon: There are many articles and studies that support the use of calcium EDTA. A great number are listed on my website. I have listed 507 abstracts that document the usefulness of oral calcium EDTA to protect lead workers from toxic exposures. Patients who have leaky gut might benefit more from oral EDTA due to enhanced absorption. Blumer and Cranton's classic article that was included in Cranton's textbook showed a 90% reduction in the incidence of cancer for patients with high levels of lead who were treated with intravenous calcium EDTA.

The reported results with IV calcium EDTA for patients with kidney failure and/or diabetes are impressive. This alone should stimulate a flood of research to examine the benefits of calcium EDTA.

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Avoiding the Cardiovascular Precipice: New Developments in Evaluation and Lifestyle Medicine

Mark Houston, MD, MS, MSc, FACP, FAHA, FASH, FACN, FAARM

Based on an Interview with Nancy Faass, MSW, MPH

Early detection and aggressive prevention and treatment of vascular disease must be implemented before any structural changes or pathology occur. To achieve this, we need to utilize new laboratory techniques, such as the advanced lipid profiles, 24-hour blood pressure monitoring, and specific tests to identify immune vascular dysfunction and markers of inflammation such as hs-CRP and myeloperoxidase. Testing is now available for oxidated and glycated MPOs and LDLs. These cholesterol particles need to be measured fairly routinely in tandem with the advanced lipid testing which is currently available from five or six different laboratories.

Vascular translational medicine also emphasizes evaluation with new imaging technologies, such as the EndoPAT, CAPWA, carotid IMT and CT Angiogram. The EndoPAT, a post-brachial artery study, is particularly noteworthy as a highly accurate assessment of endothelial function and dysfunction.

Figure 1:
Non-invasive testing for cardiovascular disease.

Functional Tests
EndoPAT (endothelial dysfunction)
CAPWA (computerized arterial pulse wave analysis)
DTM (digital thermographic monitor)
HRV (heart rate variability)
EKG and TMT
MCG (magnetocardiography)

Structural Tests
Carotid IMT/Duplex
EBT and CT Angiogram (CTA) with CAC scoring
Cardiac MRI (CMR)
ECHO (Rest and exercise)
ABI (Rest and exercise)

Other Evaluations
Cardiac PET and SPECT
IVUS (Intravascular ultrasound)
Cardiac Nuclear Studies (MPI) with PET and SPECT
Coronary Angiogram

Metabolic Factors

The blood vessel has three finite responses to an infinite number of insults. An understanding of these three responses and their downstream effects allows a new and revolutionary approach to cardiovascular disease with a focus on:

- Oxidative stress as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are increased in arteries and kidneys with decreased oxidative defense
- Inflammation increase in the vasculature and kidneys: increased C-reactive protein (CRP), leukocytosis, increased neutrophils and decreased lymphocytes, increased renin-angiotensin-aldosterone system (RAAS) in the kidney
- Autoimmune dysfunction of the arteries and kidneys: increased white blood count (WBC), and involvement of CD4+ (T-helper cells) and CD 8+ (cytotoxic T-cells).

Tracking backwards from those three finite responses brings us to the genesis of CVD with the goal of starting effective treatments to resolve downstream abnormalities.

Hypertension

Risk factors we want to address to maximize our patients' cardiovascular health and reduce heart disease include new concepts related to blood pressure (BP).

These concepts have emerged in the testing and treatment of hypertension in the last two years and current thinking in this area reflects an entirely new paradigm. It is no longer enough to simply provide patients with their results when you take their blood pressure and send them home with guidelines for self-monitoring. Those were good in the past, but they are no longer adequate to define blood pressure risk, given the expanded knowledge base in cardiovascular medicine and the technology available for clinical evaluation. We now know that the number one driving force underlying cardiovascular disease in a hypertensive patient is nocturnal blood pressure. The only practical way to monitor nocturnal blood pressure is to use a 24-hour monitoring device since most patients are not going to wake up in the middle of the night to measure their blood pressure. The new gold standard in assessment

is use of a 24-hour blood pressure monitoring device that measures:

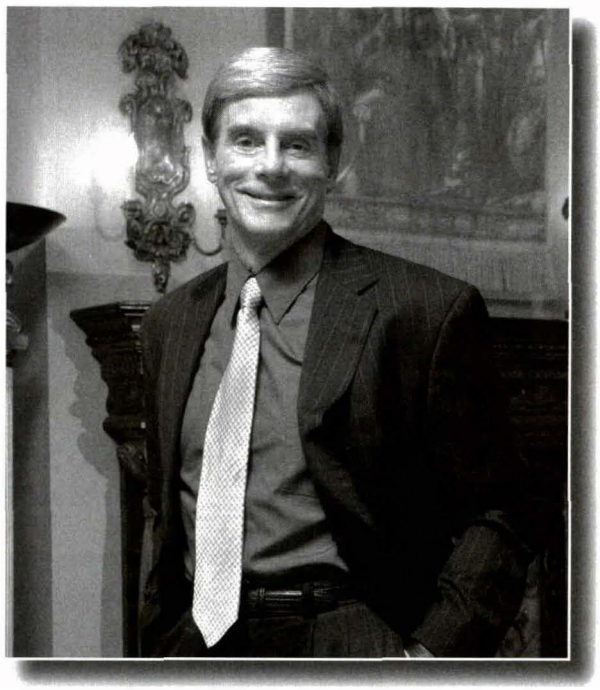
- Brachial pressure in the arm
- Central pressure in the aorta
- Arterial elasticity of the aorta and other vessels

This device also indicates whether or not there is an increase in pulse wave velocity, which indicates loss of arterial elasticity and stiffening of the arterial wall, increasing CV risk, systolic BP, augmentation index, and pulse pressure. We also use this device to assess:

- Blood pressure load (the average over 24 hours)
- Variability of BP
- Nocturnal BP
- Dipping status
- BP surges in the morning

These aspects of blood pressure function can be assessed over the entire 24-hour period while the patient is involved in normal activities and work using a 24-hour BP monitoring device. The new technology expands the information available, essentially changing all the definitions of blood pressure, arterial elasticity, and pulse wave velocity. These functions must all be measured with the new non-invasive devices, such as the mobile-o unit for central and brachial blood pressure, the EndoPAT for endothelial function, augmentation index, arterial elasticity and heart rate variability and the CAPWA for evaluation of small and large arterial compliance. This equipment is available from various companies world-wide, an entire range of devices that can be used by patients to help determine whether they have blood pressure issues or stiff arteries and whether or not they need to alter their medication.

Another new development is the finding that most blood pressure medicines should be given at night, not in the morning. The only exception would be a diuretic. The research literature indicates that giving the appropriate



Mark Houston, MD, MS, MSc

medications in the *evening* blunts some of the blood pressure surges that tend to occur in the morning and also improves nocturnal blood pressure. Simply changing the timing, without altering the dosage or the type of medications, provides an additional 25% to 50% reduction in cardiovascular risk due to stroke, myocardial infarction, and heart failure.

Dyslipidemia

The dyslipidemia story has also advanced. The measurement of total lipids is no longer acceptable; in fact, it is now obsolete. We need to know the particle size and particle number for HDL, LDL and VLDL. For HDL we want large particles and many of them. For LDL we want large particles, but not many of them. ➤

Hypertension as a Marker for Vascular Dysfunction

Only a 24-hour ABM (ambulatory blood pressure monitor) can identify specific BP risks for CVD such as nocturnal BP, dipping, non-dipping, BP surges, BP load and BP variability. Excessive dipping is associated with an increased risk of ischemic stroke and reverse dipping is associated with an increased risk of intracerebral hemorrhage (ICH). Nocturnal blood pressure is more clinically important than daytime blood pressure (27/15 mmHg difference is optimal). Morning blood pressure surges (level and rapidity) increase the risk of ischemic stroke, MI, and left ventricular hypertrophy.

It is crucial to correctly identify hypertension, given its role as a marker for vascular dysfunction. The following points should always be considered when evaluating blood pressure:

- Normal blood pressure is 120/80 mmHg, but there is a continuum of risk for CVD starting at 110/70 mmHg.
- Each increase of 20/10 mmHg doubles cardiovascular risk.
- Before age 50, diastolic blood pressure is the best predictor of risk.
- After age 50, systolic blood pressure predicts risk most effectively. The new standard of care for defining blood pressure and CVD risk is 24-hour ambulatory blood pressure monitoring, which is more accurate than office blood pressure measurements.
- Mercury cuffs are best. Electronic arm cuffs are good. Do not use wrist or finger monitors.
- Blood pressure load: Percent over 140/90 mmHg should be less than 15%.

In terms of cholesterol functionality, dysfunctional HDL is associated with a 16-fold increase in the risk of heart attacks. For example, HDL particles can be large and numerous, but if the HDL is dysfunctional, it will not protect against heart disease through its many actions and is less effective in reverse cholesterol transport. We now have new testing to determine the functionality of HDL by measuring a compound called myeloperoxidase or MPO. MPO is a marker of oxidative stress in white blood cells that causes HDL to become dysfunctional. SAA (serum amyloid A) is also a good indirect marker for HDL functionality.

In its native form, LDL is generally not atherogenic. However, LDL can also be modified into atherogenic forms such as oxidized LDL and glycated LDL. LDL that is modified is taken up by scavenger receptors on macrophages forming foam cells or plaque, as the final result of inflammatory responses in the blood vessel that cause coronary heart disease. Under severe inflammatory conditions even native LDL may be taken up by pinocytosis into macrophages and induce CVD.

Dysglycemia

Dysglycemia is another significant risk factor that has recently been redefined. Most labs report 99 mg/dL as dysglycemic. Currently a finding above 110 mg/dL is defined as metabolic syndrome, and over 126 mg/dL is considered diabetes. Those definitions have also become obsolete. Fasting blood sugar should be 75 to 80 mg/dL, and for every mg/dL above this level there is a one percent increase in the risk of heart attack. Although a blood sugar level of 100 mg /dL is considered close to normal by most labs, we now know that such a reading should actually be 75 mg/dL. Research data have shown that a reading of 100 mg/dL, previously considered within the "normal range," indicates a 25% increased risk of myocardial infarction.

Glucose tolerance testing has also been redefined. The old value for a two-hour glucose test would be 140 mg/dL, which is now considered too high. A two-hour postprandial or a two-hour glucose tolerance blood sugar should be less than 110 mg/dL That difference of 30 points now translates into a 60% increase in risk for myocardial infarction. Epidemiologically, diabetes, dysglycemia, and metabolic syndrome are increasing dramatically in this country, even in teenagers. We have to redefine the level at which patients are dysglycemic, but also realize that a great many teenagers and adults once considered healthy are actually dysglycemic, given the new guidelines.

New Approaches to Lifestyle Medicine

To truly revolutionize the management of CVD, new interventions must involve lifestyle management as well as the evaluation, treatment, and monitoring of pathophysiologic risk factors, mediators, downstream effects, and finite vascular responses.

The ABCT Exercise Program

In lifestyle medicine, exercise is currently being redefined based on new scientific evidence of how skeletal muscle actually functions to produce more than 400 different hormones, cytokines, interleukins, chemokines, and other biochemicals that influence genetic expression, reduce inflammation and oxidative stress, and support immune function. The goal is to optimize the metabolism of skeletal muscles, reducing the risk of cardiovascular disease, cancer, diabetes, and numerous other health issues. This new approach emphasizes exercise at a particular level, with specific timing, and a defined number of hours per week to achieve the production of the most beneficial hormones and affect an improvement in overall health.

Dyslipidemia Parameters

The primary driving cardiovascular risk related to LDL-cholesterol is the number of LDL-particles. HDL-P particles are most protective with larger HDL type 2b being a second important protective mechanism. Larger number and size of HDL are more efficient at reverse cholesterol transport, and more protective of the vascular system in numerous other ways. In terms of dysfunctional HDL, patients who have a HDL of 85 mg/dL or more have a greater incidence of having dysfunctional HDL that is not cardioprotective. VLDL, triglycerides, and remnant particles are frequently highly atherogenic and thrombogenic.

Current Measures of Dysglycemia

A fasting blood sugar (FBS) over 75 mg/dL increases CHD by 1% per increase of 1 mg/dL, and induces endothelial dysfunction. If a patient has an FBS of 100 mg /dL (often considered a normal level) the risk of CHD is increased by 25%. A 2-hour glucose tolerance test (GTT) over 110 mg/dL increases CHD by 2% per 1 mg/dL increase in glucose. The current definition of an abnormal 2-hour GTT is >140 mg. If a patient's result is 140 mg, which again is currently classed as "normal," CHD and MI are increased by 60%. Hyperinsulinemia is also an independent risk factor for CHD. Insulin resistance creates inflammation, reduces nitric oxide levels, and causes endothelial dysfunction and vascular disease through the mitogen-activated protein kinase (MAPK) pathway, which is atherogenic and induces hypertension as opposed to the phosphatidylinositol 3-kinase (PI3K) pathway, which is anti-inflammatory, anti-hypertensive, and anti-atherogenic.

This new approach, ABCT, stands for aerobics, build, contour, and tone. The program is designed for both men and women to achieve good health, but also toning and bulking (if desired), and the maintenance of a good physical appearance. The inner aspect of this work employs skeletal muscle fitness to improve the health of the patient. The basic program is fairly simple, involving one hour per day maximum training, because more than that results in over-training syndrome. The first phase is resistance training performed in the morning, for at least 40 minutes in a fasting state. Follow-up to resistance training involves 20 minutes of aerobics.

Resistance Training

For the resistance training any type of weights can be used. It is very important to rotate the weight training regimen using different muscle groups each day, focusing on either various muscle groups singly or in combination to maximize the intensity of resistance. That aspect of the program is performed in 40 minutes of intense exercise, waiting about 60 seconds between each of the different movements. The resistance training is comprised of five different exercises, varied every day, each one performed very quickly. For example, to do the bench press:

- The weight is maximized for 12 reps
- The weight is dropped by 25% for 18 reps
- Drop the weight again by 25%, done in 50 reps
- Go back to maximum weight and do 12 reps
- Wait one minute between each of these reps

There are five repetitions, but at different weights, maximizing both the intensity of the weight, and also the number of repetitions by varying the amount of weight and resistance. That regimen is applied in working with each muscle group—biceps, triceps, or leg presses. The goal is to do at least two or three muscle groups in the upper body and two or three in the lower body at each 40-minute exercise session.

Aerobic Interval Training

The aerobic training that follows is performed as fast as possible using the exercise of choice, whether that involves running, biking, or swimming. In these sessions:

- Exercise for about 30 to 60 seconds at approximately 80% to 90% of maximum aerobic capacity.
- Do that set about three times (1.5 to 3 minutes for each set) at about 50% of maximum aerobic capacity to allow the body to recover.
- Repeat that set about six times, 30 to 60 seconds on.
- Then do those double sets three times at the lower MHR (maximum heart rate) six times and that completes the regimen.

The entire set of exercises is finished at the 60 minute mark. During exercise, obviously we want to have good water and hydration, but also proper nutrition before, during, and after we work out. We pair the exercise program with a nutritional program that balances the proper types of carbohydrates and protein, and nutrients such as whey protein, carnitine, taurine, and d-ribose, as well as a generous intake of fluids. After finishing the exercise, we want to assure plenty of good, healthy food to maximize muscle recovery following the work out. That is the exercise program in a nutshell, exercising in sync with human genetic hardwiring. This means increasing muscle mass and decreasing body fat. Body composition is important beyond the specifics of weight; for example, ideal composition means less than 16% total body fat. Since visceral fat drives cardiovascular risk, visceral fat should be below 16% for men and 22% or less for women.

Paleo and Mediterranean Diets

The second important aspect of the program is overall nutrition. This approach incorporates the best elements of the Mediterranean and Paleolithic diets, which have been shown to maximize nutrient-genetic interaction and support healthy genetic expression. Since our genes are 99% identical to those of our Paleolithic ancestors, we want to assure that dietary nutrition reflects that genetic makeup by including key aspects of Paleolithic nutrition. The bottom line is quite simple: at least ten servings of fruits and vegetables per day, primarily vegetables:

- Six servings of vegetables
- Four servings of fruit. However, if blood sugar or prediabetes is an issue, obviously less fruit should be consumed.

The vegetables and fruit should be relatively uncooked or raw, depending on the digestive competence of the individual and the specific foods selected. Organic foods with a range of colors and nutrients are preferred. Refined carbohydrates are eliminated or reduced dramatically, including starches, sugars, potatoes, white rice, and all breads.

Wheat gluten can be deadly, and many people have dairy sensitivities. All types of high quality organic protein are recommended, from both vegetable and animal sources: cold water fish; organic turkey; organic chicken; and organic, lean, grass-fed beef. Ideal protein content is between 1.5 and 2 grams per kilogram of body weight, depending on age and level of exercise.

Perspectives on Sleep

Current thinking suggests that we need to sleep eight hours every night. Seven hours is not enough and nine hours is too much. Too much sleep is counterproductive,

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as is too little sleep. Eight hours of sleep is associated with reduced risk of diabetes, heart disease, Alzheimer's disease, and obesity—the list goes on and on. It is not only that eight hours is important: what time we go to bed and when we get up are also significant. Circadian rhythm of the human body correlates with the presence of sunlight, so we want to go to bed as the sun is setting, and get up when the sun is rising. That means optimal bedtime is typically between 8 and 10 p.m. depending on the season of the year. Tack eight hours onto that and get up eight hours later. A typical sleep schedule could be 8 p.m. to 4 a.m. or 9 to 5 or 10 to 6, depending on the time of year. The recommendation is to keep that sleep schedule relatively steady during the year so one's biologic clock stays within a circadian rhythm that maintains good health. People who do not sleep the right amount are more prone to diabetes, weight gain (particularly in the visceral area), high blood pressure, cardiac arrhythmia, heart failure, myocardial infarction, strokes, and numerous other problems.

Reducing Sympathetic Overdrive

The final strategy is stress reduction. Stress is currently an enormous issue in our society. People tend to experience sympathetic overdrive, resulting in adrenal exhaustion over time. The function of the parasympathetic nervous system and vagal tone are downgraded, promoting increases in blood pressure, arrhythmias of the heart, heart disease, and other cardiovascular issues. Rebalancing the sympathetic and parasympathetic nervous systems is extremely important.

- The parasympathetic nervous system can be reset to some degree with rhythmic deep breathing exercises. This means performing deep breathing frequently during the day (five second inhalation, five second exhalation).
- RESPeRATE is a machine that allows patients to re-track and reset their breathing rhythm so they can time it, understand it, and retrain themselves. This is useful for downgrading sympathetic tone, with the potential to reduce numerous cardiovascular problems.

The most common issues that we can measure effectively are heart rate, heart rate variability, and heart rhythm variability. Heart rate should be irregular when timed in milliseconds. If it is not irregular, that indicates greater risk of heart disease.

- Various devices such as Heart Smart and EndoPAT measure heart rate variability quite accurately. If sympathetic tone is overbearing parasympathetic tone, that needs to be corrected to reduce cardiovascular risk.
- The other test we use is heart rate recovery time following a treadmill test, measured by exercising until heart rate achieves a certain level. With rest, that rate should drop very quickly, an indication that parasympathetic tone is appropriately reducing heart rate, documented in a timed event. If heart rate is not reduced by at least 12 to 16 beats per minute once exercise is completed, that suggests increased risk for a cardiovascular event. A maximum heart rate of 180, for example, should return to baseline in increments of 16 beats per minute: i.e. within five minutes or so.

If patients use the strategies described here, that could prevent 70% to 80% of all cases of heart disease in the United States. The other 20% of events are exacerbated by genetic risks and hundreds of other complex, but minimal risk factors beyond the scope of this discussion. Research has shown that all the other risks are minor in comparison to these primary risks, so it is important to define them correctly, identify outliers, and treat them correctly.

Conclusions

In terms of clinical experience, we find that once patients get involved in these lifestyle programs, working with a nutritionist and an exercise physiologist, the program is quite easy to manage. Real improvement begins to occur when patients start eating better, reducing carbs, and in many cases eliminating gluten. The two most difficult factors for the majority of people are getting eight hours of sleep and reducing stress. Exercise in particular helps patients sleep, and tends to relieve stress. The first steps in an effective program involve the evaluation and management of hypertension, lipids, and glycemic levels. Exercise and nutrition are now key components of this medical management. The final elements, sufficient sleep and stress management, usually fall into place once those initial issues progress.

About the Author

Dr. Mark C. Houston graduated from Vanderbilt Medical School, completed his internship and residency at the University of California at San Francisco, and then returned to Vanderbilt University and Medical Center, where he continues to teach and practice. Dr. Houston is triple-board certified by the American Board of Internal Medicine (1977), the American Society of Hypertension (ASH) as a specialist in clinical hypertension (FASH) (2000), and the American Board of Anti-Aging Medicine (ABAAM) (2000). He also holds a Master's of Science Degree in Human Nutrition (2003) and a Master's of Science in Metabolic and Nutritional Medicine (2012). Dr. Houston is on the Consulting Editorial Board or is a consulting reviewer for more than 20 major U.S. medical journals. He serves as Chair of the Medical Advisory Board of the American Nutraceutical Association (ANA), and Editor-in-Chief of their journal (JANA). Dr. Houston has presented more than 10,000 lectures on hypertension nationally and internationally, and published over 175 articles and scientific abstracts in peer-reviewed medical journals, as well as textbook chapters, handbooks, and films. He has also completed over 70 clinical research studies in hypertension, hyperlipidemia, and cardiovascular disease.

Publications

The ABCT Exercise Program. The specifics on this program are available from two sources. One is a recent book by Mark Houston, MD, entitled *What Your Doctor May Not Tell You about Heart Disease* published by Grand Central Life & Style (Grand Central Publishing). The book can be obtained on Amazon, through the publisher directly, or in local book stores. Members of the American Board of Integrative Holistic Medicine can obtain the ABCT exercise program in the *Curriculum Study Guide 2013* online at http://www.abihm.org/study-guide. The cost to nonmembers is $150.

Books. Other best-selling books by Dr. Houston include *The Handbook of Hypertension* (Wiley-Blackwell, 2009), *Vascular Biology in Clinical Medicine* (Hanley and Belfus, 2002), and *What Your Doctor May Not Tell You About Hypertension* (Time-Warner Books, 2003).

Resources on the web. Integrative medicine protocols are available at www.hypertensioninstitute.com under "Supplement Recommendations" and also at http://www.hypertensioninstitute.com/integrative-medicine. Journal articles available at no cost on nutraceutical therapies can be accessed by searching PubMed for "Houston MC".

Editorial

Nancy Faass is a writer and editor in San Francisco who has worked on more than 40 books for publishers that include Elsevier, Harper, McGraw-Hill, Mosby, New Harbinger, New World Library, North Atlantic, and others. Director of The Writers' Group, her work includes writing for the web, and work on articles and white papers. For more information see www.HealthWritersGroup.com.

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Vascular Biology, Endothelial Function, and Natural Rehabilitation
Part 1: The Nitric Oxide Pathway

by Jeremy Mikolai, ND

The endothelium covers the inner surface of blood vessels. It is the interface between the elements of the blood and the walls of blood vessels. It is a single cell layer thick and is composed of squamous endothelial cells. This tissue covers the inner surface of every artery, arteriole, capillary, venule, and vein in the body as well as the inner surfaces of the heart. It is the body's largest paracrine organ; laid out cell to cell, the endothelium of an average-sized human being would cover 700 m2.[1]

From the time of its discovery in the 1600s by Malpighi, the endothelium was considered an inactive physical barrier between the walls of vessels and the flow of blood.[2] Recent decades of advancement in the study of vascular biology and endothelial function have revealed that the endothelium is the site of dynamic interplay. Endothelial signaling is responsible for changing blood vessel sizes and pressures; it is responsible for the formation and breakdown of clots and platelet plugs. Inflammation, oxidized cholesterol, endothelial damage and repair, connective tissue degradation and deposition, atherosclerosis, and acute cardiovascular events all play their part in endothelial function and dysfunction.[3]

In health, the endothelium maintains appropriate wall tension and permeability of the blood vessels; maintains an anticoagulant, antithrombotic, profibrinolytic milieu that also inhibits immune cell adhesion and activation; and it maintains and promotes appropriate vascular remodeling.[3] *Endothelial activation* is the term for a change in homeostasis including gene expression, tissue repair, and inflammatory mechanisms resulting from injury. Activation of the endothelium results in the expression and exposure of myriad procoagulant and platelet aggregating factors, adhesion molecules, selectins, integrins, therefore promotion and propagation of endothelial dysfunction.[4,5]

Endothelial dysfunction has been succinctly and deftly defined by Corretti, Panjrath, and Jones as "regulatory changes leading to abnormal vasomotion and the expression of a prothrombotic and proinflammatory phenotype of the vascular endothelium."[1] It may include many changes in the gene expression, molecular expression and signaling, phenotypic cellular expressions, immune activation, and mechanical alterations to the tissues of the vascular system.

Dysfunction of the vascular endothelium is central to the pathogenesis of many acute and chronic conditions.[6] Like the endocrine, immune, hematologic, and nervous systems, it is intimately involved, directly or indirectly, in many pathological processes. Endothelial dysfunction has diverse pathological manifestations which may be acute or chronic; they may be insidious, emergent, or both; they may involve the heart and vascular system or any other organ system.

The acute disruption of the endothelium overlying a vulnerable atherosclerotic plaque is the most common cause of an acute myocardial infarction.[7] A rapid, life-threatening, and highly fatal form of pulmonary edema called acute or adult respiratory distress syndrome (ARDS) can result from injury to the respiratory endothelium or epithelium of the lungs.[8] Endothelial function plays a role in the both acute blood clots and hemorrhages. It has a central role in chronic and recalcitrant high blood pressure, atrial fibrillation, and the propagation of airway remodeling in asthma and COPD.[9]

Vascular endothelial (VE) cells that are acutely injured or succumb to chronic exposure become senescent, go through apoptosis, and are released into circulation.[10] The VE repair mechanisms depend on endothelial progenitor cells recruited from the bone marrow or the replication of local mature endothelial cells.[11] In acute endothelial injury, there may be an increase in the number of these

cells available in the circulation, but in chronic endothelial dysfunction, the availability of endothelial progenitor cells may become depleted. Progenitor endothelial cells recruited to an area of injury can participate in endothelial repair and mature into functional VE cells. However, in an inflammatory milieu, these cells can also differentiate into macrophages which participate in further endothelial dysfunction, destruction, and inflammation.[1]

The vascular milieu greatly affects endothelial function and propagation of atherosclerotic disease. High levels of free fatty acids (FFA) in the blood, high levels of plasma glucose, high levels of remnant lipoprotein particles (RLP), oxidized low-density lipoprotein cholesterol (ox-LDL-c), and others impair the vasomotor function of the VE, and they promote and propagate atherosclerotic cardiovascular disease (ASCVD).

We encourage our students to think about ASCVD as a disease that affects the entire organism. Atherosclerotic vascular disease in any vessel in the body portends atherosclerotic disease in other vessels in the body. Atherosclerotic diseases have nearly identical pathophysiology, risk factors, and consequences; they differ only slightly by their location and therefore by the downstream consequences of their effects. Atherosclerosis and endothelial dysfunction are inexorably intertwined, and the consequences of atherosclerotic disease and those of endothelial dysfunction are one and the same.

The nitric oxide (NO) pathway is central to all elements of endothelial function and signaling. The role of inflammation and inflammatory mediators, neurohormonal mediators, vascular remodeling, and the redress of those factors through natural medicine treatments are conversations that extend organically from a core understanding of the NO pathway. As such, we will take our discussion in two parts. The remainder of the present discussion will focus on the NO pathway and its rehabilitation in endothelial functioning. The second part of this article, to be published later, will address the remaining principles of endothelial dysfunction.

The hypothesis about an endothelial-derived relaxing factor dates back to the early 1980s to the work of Furchgott and Zawadski. They demonstrated that vascular relaxation in the presence of agents such as acetylcholine (ACh) depends on the action of another mediator, NO.[12] NO is the primary relaxing factor for the VE and a primary component in the vasomotor activities of the vascular system; its contributions to appropriate vascular function and its role in VE dysfunction are far wider reaching.

The NO molecule is produced both at a continuous low-level concentration (basal secretion) and at increased amounts in response to various stimuli. Basal NO maintains the resting tone of the vascular system and is responsible for maintaining an antiatherogenic, antithrombotic state. It decreases oxidation of LDL cholesterol, vascular smooth muscle cell proliferation, expression of adhesion molecules, platelet aggregation, and extracellular matrix production in the setting of healthy endothelial function.[3,13] By contrast, activated endothelium produces procoagulant/prothrombotic molecules such as tissue factor, von Willebrand factor (vWF), and platelet activating factor (PAF).[14] NO has important anti-inflammatory and antiproliferative properties modulated through its inhibitory signaling on nuclear-factor kappa B (NFkB), and this modulation also decreases production of the potent vasoconstrictor endothelin-1 (ET-1).[15,16] NO participates in immune function as a reactive nitrogen species, as well as in apoptotic signaling, in neurotransmission, and in the recruitment of new endothelial progenitor cells.

The NO molecule is produced as a result of several stimuli. The mechanical stimulus of pulsatile flow and sheer stress against the vascular walls results in the release of vasodilator mediators including NO and prostacyclin (PGI2). The vasodilatory effects of NO are mediated by its activation of second messenger systems which close calcium (Ca) channels on vascular smooth muscle cells which surround blood vessels. Decreased concentration of Ca leads to decreased muscle contraction and relaxation.

The nitric oxide molecule (NO) is produced predominantly in the caveolae, invaginations in the surface of the endothelial cells. The amino acid L-arginine (Arg) is the substrate for production of NO; the catalytic action of the enzyme nitric oxide synthase (NOS) turns Arg into NO and the amino acid L-citruline. The NOS enzyme activity is controlled by the regulatory protein caveolin 1. Caveolin 1 binds to the protein calmodulin, which results in inhibition of NOS. When Ca binds to calmodulin, caveolin 1 is displaced and NOS production of NO commences. The release of Ca promotes muscle contraction and the release of NO, which in turn decreases muscle contraction.[13,17]

The NOS system is a family of isoenzymes. NOS enzymes depend on the cofactors nicotinamide adenine dinucleotide phosphate (NADPH), and tetrahydrobiopterin (BH4).[18] The NO molecule itself is a lipophilic free radical with moderate water solubility; therefore, it diffuses readily through both the cell membrane and the cytosol. The NO radical readily reacts to form other reactive oxygen and nitrogen species (RONS) capable of producing oxidative damage, destruction of extracellular matrix (ECM) and connective tissue in the subendothelial space.[19] The inducible NOS (iNOS) is transcribed and produced in many different tissues and in response to various cytokines and bacterial products; it may be used by immune effector cells to produce NO radicals for host defense. Neuronal NOS (nNOS) produces NO to be utilized for neurotransmission.

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NO Pathway

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NO is used in cell signaling by both the central and peripheral nervous systems.[20] It is the endothelial NOS (eNOS) that concerns us most in this discussion of endothelial function.

Decreased NO availability is a core component of endothelial dysfunction. The activity of NO typically becomes reduced by one or more of four mechanisms: decreased eNOS expression, eNOS uncoupling, increased NO scavenging, impaired NO signaling.[21,22]

The expression of eNOS, its transcription and production are modified by diverse stimuli. Mechanical shear stress and hydrostatic pressure stimulate expression. Hydrogen peroxide, as well as several growth factors (vascular endothelial growth factor, TGF-beta, basic fibroblastic growth factor, and epidermal growth factor) and hormones (angiotensin II and endothelin 1) stimulate eNOS expression. The expression of eNOS is inhibited by the presence of NO, oxidized LDL, the cytokine TNF-alpha; it may be increased or decreased by erythropoietin.[22,23]

When there is a deficiency in either Arg or BH4, the action of eNOS switches from production of NO to production of other RONS; we refer to this switch as e*NOS* uncou*pling*.

In the setting of BH4 deficiency, eNOS predominantly generates the superoxide anion (O2–); when Arg is deficient there is substantial production of hydrogen peroxide (H2O2). The NO radical rapidly reacts with the O2– radical to produce the peroxynitrite radical (ONOO–). This radical is important for several reasons: first, it is extremely damaging to tissues and is implicated in diverse diseases from diabetes to osteoarthritis; second, by virtue of using up the NO molecule it makes NO less available; third, ONOO– decreases BH4 and therefore inhibits production of further NO.[24,25]

In the setting of increased oxidative stress, the scavenging of NO by other RONS is further increased and NO levels further decreased. The increased inactivation of NO by RONS decreases available NO, even if NO does not participate in production of further radicals. Increased oxidative stress and impaired endothelial function typically coexist as elements of the same conditions, as in coronary heart disease and cardiovascular risk factors such as diabetes, tobacco use, dyslipidemia, dysglycemia, and others. In coronary disease, increased oxidative stress is partly the result of the increased action of NADPH-oxidases, xanthine oxidase (XO) enzymes, and increased O2– production. Endothelial dysfunction and oxidative stress result in further NO impairment and endothelial dysfunction begets more endothelial dysfunction.[21,22,26,27]

This mechanism, oxidative stress and redox injury on the NO pathway resulting in decreased NO production or increased NO degradation, is generally accepted as being the predominant mechanism of endothelial dysfunction.[6] Further elaboration of this mechanism, it contributors, its consequences, and its interplay with the neuroendocrine system is a necessary undertaking, but at a later occasion.

Several biologically important competitive inhibitors of eNOS exist. Along with several ways described above, the inhibition of eNOS production of NO by endogenous and exogenous molecular competition is an important mechanism of decreased NO signaling. The eNOS enzyme is inhibited by the endogenously occurring asymmetric dimethylarginine (ADMA), geranyl-geranyl pyrophosphate (GPP), and NG-monomethyl-L-arginine (L-NMMA) molecules; the L-NMMA molecule and the related compound L-nitroarginine methyl ester (l-NAME) are also important pharmacologic inhibitors of eNOS. The GPP molecule is an intermediate in cholesterol synthesis and represents another mechanism by which dyslipidemia provokes endothelial dysfunction.[20]

The ADMA molecule is produced by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), and that redox sensitive enzyme activity is increased in the setting of oxidative stress, further inhibiting eNOS activity.[20] The ADMA molecule binds to eNOS, but does not produce NO. As a result, it slows the conversion of Arg to NO. Increased ADMA production is triggered by vascular shear stress, like NO. Increased ADMA also occurs as a result of a large number of health conditions, many of which are associated with endothelial dysfunction.[20,28,29] Thus, endothelial dysfunction begets endothelial dysfunction. Arg and ADMA have a similar metabolic fate, conversion to L-citruline, and that shared fate may have clinically utility for us.

Flow mediated dilation (FMD) and changes in arterial blood flow are good markers of endothelial function. Other biomarkers exist and can be tested in the blood; other physical metrics of arterial flow and vascular tone, such pulse wave analysis, exist and can be tested. There are several techniques available for measuring FMD, but at their core, each technique seeks to increase blood flow to a distal artery by either delivering a pharmaceutical vasodilator or by creating shear stress on the proximal artery. To increase shear stress, blood flow to the distal aspect of the artery is restricted. When the obstruction to blood flow (usually a blood pressure cuff) is removed, the response of healthy endothelium is reactive dilation of the artery and a period of increased blood flow. Change in artery caliber and blood flow can be measured by any of several types of instruments.

Studies using FMD have helped to elucidate the endothelial dysfunction that occurs with several cardiometabolic risk factors and dietary habits. There is a strong relationship between blood levels of cholesterol and decreased vasomotor response in the coronary

arteries. Vita et al. (1990) showed an extremely significant ($p = 0.0003$) decrease in coronary artery diameter change in response to acetylcholine (ACh) with increasing levels of total cholesterol (TC). An even stronger relationship between traditional ASCVD risk factors and coronary diameter change in response to ACh became apparent in this study. For each additional coronary risk factor present, the coronary vessel diameter change was dramatically impaired ($p < 0.0001$).[30] Kugiyama et al. 1998 demonstrated a similar finding with respect to elevated levels of remnant lipoprotein cholesterol (RLP) in the blood; the percent change in coronary artery diameter in response to ACh drops precipitously as the RLP level increases ($p = 0.0001$).[31] Impaired endothelial function and change in blood flow resulting from dyslipidemia is a consistent finding. Creager et al. (1992) demonstrated significant reduction in forearm blood flow change in dyslipidemic individuals when compared with healthy controls.[32] Hyperglycemia produces a similar significant decrease in forearm blood flow change in response to the vasodilator methacholine. Compared with healthy volunteers with normal blood sugar, volunteers with high blood sugar have an impaired endothelial response to vasodilation that is most pronounced at the highest flow measurements.[32]

The rehabilitation of endothelial function relies, first and foremost, on the modification of the same basic cardiometabolic and atherosclerotic cardiovascular disease risk factors that are omnipresent. Studies of the effects of diet, antioxidants, statins, ACE inhibitors, and hormone replacement on endothelial function have all been successful.[33–36] However, no study has yet shown that improvement of endothelial dysfunction changes hard end points, namely cardiovascular morbidity and mortality. Those data do not exist because the studies have not been done. Likewise, endothelial function testing is not yet considered to be clinically relevant because studies demonstrating its prognostic value against hard outcomes are yet to be accumulated.

Statin drugs are the standard of care for the redress of many ASCVD risk factors and have simultaneous side benefits on endothelial function. With the 2013 ACC/AHA updated guidelines on management of dyslipidemia and cardiac risk, statins are mentioned in the absence of other lipid modification agents. Again, this is so because statins have demonstrated significant effects against cardiovascular morbidity and mortality; their effects on vessels walls would be considered a side benefit. Beyond treatment of dyslipidemia, statins improve endothelial function through increased NO availability; decreased radicals, immune effector cells, and inflammation; decreased coagulation and platelet aggregation; decreased ECM deposition and degradation; healthy vascular remodeling; and decreased neurohormonal stressors.[37]

Diet is foundational to endothelial function. We have seen that high fat and sugar in the blood promote endothelial dysfunction. A Mediterranean diet is high in polyphenols from fruits and vegetables and promotes healthy endothelial function. This includes promotion of NO and endothelium-derived hyperpolarizing factor (EDHF), which may contribute to the overall antihypertensive and cardioprotective effects of polyphenol rich foods.[38] A small crossover study of 19 volunteers eating 70 g/day of tomato paste (33.3 mg lycopene) for 15 days demonstrated significant increases in FMD of 3.3%.[39] A trial of 42 healthy volunteers consuming a biofermented nutraceutical product, 3 grams three times/day for six weeks, demonstrated significant increases in FMD (approximately 3%), as well as significant increases in plasma NO and decreases in ADMA after consumption.[40] A 2012 meta-analysis of 16 studies including 901 patients and investigating omega-3 (n-3) fatty acid consumption effect on FMD, demonstrated a significant and robust protective effect of n-3 on endothelial function and increases in FMD of 2.3%.[41]

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There is a solid foundation of evidence for the role of dietary and supplemental polyphenols in endothelial function. Individually, there is stronger evidence for some than for others. Red wine, grapes, berries, cocoa, pomegranate, black and green tea, coffee, olive oil, soy, quercetin, and berries all have degrees of literature support for their use to improve endothelial function[42] Two double-blind crossover trials of 21 healthy men investigated the effects of blueberry flavonoid intake on FMD. At any dose greater than 766 mg blueberry polyphenols, significant increases in FMD were observed at 1, 2, and 6 hours after consumption and were correlated to circulating metabolites and decreases in neutrophil NADPH oxidase activity.[43] Short- and long-term studies of an anthocyanin isolate from berries (320 mg) in hypercholesterolemic patients demonstrated significant short-term and long-term improvements in FMD and long-term increases in cGMP.[44] A 30 day double-blind, crossover study of 24 men with metabolic syndrome examined the effects of freeze-dried grape polyphenol powder verses placebo on measures of endothelial function. On-treatment effects demonstrated significant decreases in systolic blood pressure (SBP), and adhesion molecules sICAM-1, and sVCAM-1 and a highly significant increase in FMD ($p < 0.0001$).[45] Studies of cocoa, flavanol-rich chocolate, and dark chocolate have demonstrated positive effects on endothelial function, blood pressure- and platelet function.[46]

Ginkgo biloba extract has demonstrated important effects on coronary and brachial artery blood flow in patients with coronary artery disease. In a study of 80 patients, ginkgo extract significantly increased left anterior descending coronary artery blood flow in maximal

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systolic and diastolic peak velocity and diastolic time velocity integral measures; brachial FMD was increased 69.8%.[47] Thus, ginkgo may be an important adjunct therapy for patients with known ASCVD.

Supplementation with NO substrates or intermediates such as the amino acids Arg or L-citruline can rehabilitate NO production and endothelial function. Supplementation of 2 g of Arg, 3 times daily in 38 patients with lower extremity peripheral arterial disease (PAD) and concomitant diabetes mellitus type 2 (DM2) was shown to significantly increase NO levels and total antioxidant status (TAS) as compared with controls over a 2-month trial.[48] Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a reasonably common type of mitochondrial disorder which has been associated with decreased NO availability. Supplementation with Arg and L-citruline in this population has demonstrated increased arginine synthesis, increased plasma concentrations of the two amino acids, and increased NO production. The effects were more pronounced with citruline supplementation than with Arg.[49]

Coenzyme Q10 (coQ10) has been repeatedly demonstrated to increase FMD in patients with CVD and endothelial dysfunction. Doses of 200 to 300 mg used over 8 to 12 weeks in DM2 patients on statin drugs and in patients with ischemic left ventricular systolic dysfunction (LVSD) have been shown to significantly improve FMD. In LVSD, CoQ10 also significantly decreases lactate/pyruvate ratio. It also reduces the impact of oxidative stress on NO production. CoQ10 may reduce O2– and ONOO– inactivation of NO and protect against nitrosative damage and oxidation of LDL. Investigations demonstrate that treatment effects are greater in patients with the lowest levels of extracellular superoxide dismutase (ecSOD), which implies that greater improvement is seen in setting with the highest oxidative stress.[50-52]

Reduced folate and uric acid can scavenge the ONOO– radical. Folate has been shown to reconstitute the appropriate activity of uncoupled eNOS and to scavenge the nitrogen dioxide and carbonate radicals derived from ONOO–.[53] A study of the effects of 5-methyltetrahydrofolate (5-MTHF) on the rehabilitation of endothelial dysfunction was done with 56 patients undergoing coronary bypass graft (CABG). An IV infusion of 5-MTHF resulted in improved NO-mediated vasomotor response, reduced O2– levels, strong ONOO– scavenging, reversal of eNOS uncoupling by several measures, enhanced eNOS activity, and increased vascular BH4 levels.[54] In turn, BH4 helps to improve the FMD response to the hyperglycemic state. In a small crossover study, patients were given either active BH4 or its inactive isomer during a 2-hour 75 g oral glucose challenge. Glucose loading impaired FMD, but that impairment was reversed by BH4 supplementation and not supplementation of its isomer.[55]

Melatonin has important effects in the NO pathway. Melatonin is a scavenger of the NO radical and contributes to antioxidant activity in both aqueous and lipid biological compartments. Melatonin scavenges several other radicals, including hydroxyls, H2O2, peroxyls, singlet oxygen, and ONOO–. Melatonin also inhibits the activity of NOS, which may increase its indications in acute oxidative injury.[56]

Several natural substances show compelling antioxidant and radical scavenging activity and upregulation of eNOS expression, in vitro. *Salviae mitiorrhizae* radix and its constituent ursolic acid, *Zizyphi spinosae,* and its constituent betulinic acid, *Cynara scolymus,* and its constituents luteolin and cynaroside, and *Prunella vulgaris,* which shares these constituents, all demonstrate significant increases in eNOS expression, in vitro.[57] Several constituents in red wine significantly increase eNOS expression, including cinnamic and hydroxycinnamic acids, cyanidin, and phenolic acids. However, the predominant and most efficacious stimulator of eNOS expression and transcription presently in our arsenal and our wine continues to be trans-resveratrol.[58]

One of the great beauties of natural medicine is its elegance, its ability to address the underlying causes of disease, and often many of them at once. The vascular endothelium and its function may not yet be an official target of therapy, but endothelial dysfunction is the unified field theory of all forms of cardiovascular disease and several non-cardiovascular diseases. Dysfunctional endothelium has to be rehabilitated or it will continue in an inevitable progression of increased dysfunction and disease. Fortunately, in natural medicine, it is a relatively simple matter to choose treatments that have side benefits on improving endothelial function.

The NO pathway is the first half of the story of endothelial dysfunction. We will soon see that inflammation and the changes that it imposes upon the endothelium, on other cell types, and on production of other mediators are also central to the pathogenesis and progression of endothelial dysfunction. We will see the role of neurohormonal stressors on those processes, and how we might rehabilitate them using natural medicine.

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Notes

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Oxygen Multistep Therapy Enhancing Intracellular Oxygen: A Case Study

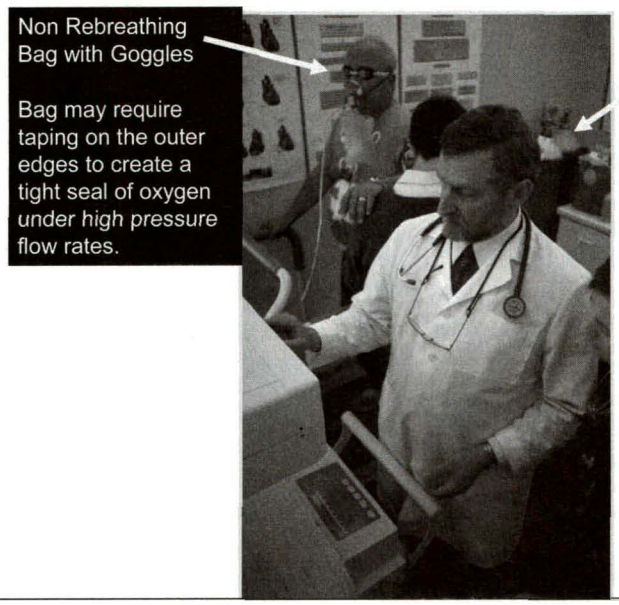
by Martin Milner, ND, and Janna Redding, ND

Cellular health determines the health of the organism, and oxygen plays a crucial role in optimum cellular development, maintenance, and repair. The extent of diseased tissue is in part determined by how long it has been deprived of optimal intracellular oxygen.[1] Clinical treatments focused on enhancing delivery and cellular uptake of oxygen may prove useful in the treatment of diseases associated with vascular compromise and/or chronic hypoxia. Below we present a technique called oxygen multistep therapy (OMST). OMST was developed by German physician and researcher Dr. Manfred von Ardenne et al. in the 1970s to facilitate the utilization of oxygen while improving endothelial cell dysfunction and reducing endothelial cell adhesion.[2]

What is Oxygen Multistep Therapy?

OMST has been implemented in various clinical settings to promote healing and regeneration of tissues. Dr. Martin Milner, medical director at the Center for Natural Medicine (CNM) in Portland, Oregon, was introduced to OMST in 1983 by Dr. Marvin Schweitzer. Schweitzer, speaking fluent German, had the opportunity to train directly with von Ardenne in Eastern Europe, where he learned different OMST techniques.

Oxygen Multistep Therapy in Action



In his publication *Oxygen Multistep Therapy: Physiological and Technical Foundations,* von Ardenne explained how OMST produces its remarkable effects. By the patient's exercising while breathing high flow rates of oxygen, an arterial pressure and cellular oxygen regulating mechanism occurs that von Ardenne refers to as a "switching mechanism" at the microcirculation level and greatly increases the amount of oxygen delivered to cells.[3]

In an ideal situation, the pressure of oxygen in the arteries will be almost the same as the pressure in the alveoli. This is the case in younger individuals. However, with age, the arterial pressure of oxygen declines and the amount of oxygen that is able to enter the cell is diminished.[4] OMST helps raise the arterial pressure of oxygen back to youthful levels. Furthermore, von Ardenne proved that after OMST, the pressure of oxygen (pO2) in the arterioles increased while venous pO2 is reduced, confirming increased uptake of cellular oxygen.[5] Research starting in 1977 demonstrates the effectiveness of this therapy in a variety of clinical settings, and OMST techniques are now employed worldwide.

Indications

OMST may be helpful for the following conditions: coronary artery disease (with or without angina), post-stent deployment or CABG (coronary artery bypass graft)

procedure, intermittent claudication, and peripheral artery disease. It promotes accelerated wound healing after operation or infection and may prevent the necessity of amputation. It may also improve cancer outcomes, mental acuity, macular degeneration, hepatic failure, and migraines.[2]

Hypothetically OMST could be considered a third-line treatment after high flow rates of oral oxygen or hyperbaric oxygen therapy for carbon monoxide poisoning. Additionally, improvements may also be seen in small vessel coronary artery and peripheral vascular disease, stroke rehabilitation, and in exercise performance reserve that has been impaired by lack of activity after a serious illness. At CNM we also use OMST as an adjunctive therapy in certain cancer patients and to enhance athletic performance in elite athletes.

Potential Contraindications

Precaution should be taken with those who have underlying lung compromise such as chronic obstructive pulmonary disease (COPD). Recent studies have shown that when COPD patients who have chronically compensated elevated CO2 levels (known as "CO2 retainers") are in respiratory compromise and are put on high flow supplemental oxygen, the CO2 in their blood may increase.[6,7] This can further inhibit their hypercarbic drive and either put them into respiratory failure or worsen their current level of respiratory distress. We therefore recommend that all individuals with risk factors for lung disease perform pulmonary function testing before engaging in OMST. At CNM we have developed low flow oxygen delivery modifications, allowing us to safely use OMST with many COPD patients while carefully monitoring for changes in oxygen saturation during and after exercise.

OMST Procedure in the Clinical Setting

After the patient's lung function has been confirmed to be within normal limits with spirometric testing, the patient is exercise tolerance tested (ETT). Depending upon the patient's activity limitations, a treadmill, a recumbent bicycle, or an arm bicycle machine is used as exercise equipment. ETT is then performed at a target aerobic heart rate of 50% to 80% of maximum heart rate prior to participation in OMST or any other exercise-based cardiac rehabilitation program. After OMST or cardiac rehabilitation is completed, intermittent and ongoing ETT is strongly recommended and may be repeated as changes in the patient's clinical condition warrant.

One of the many OMST exercise protocols involves the patient's being primed with oral and sublingual nutrients before the procedure. These agents help the uptake and utilization of oxygen, and are customized for each individual based on his/her presentation and problem list (see Table 1). In our standard protocol, the patient's target aerobic heart rate is then calculated at 50% to 80% of maximum heart rate. Oxygen is delivered through a non-rebreathing bag at high flow rate of 15 to 25 liters per minute. The edges of the oxygen mask are sealed with tape and the patient's eyes are protected with goggles. Eye goggles are worn to eliminate the risk of high flow oxygen leaking through the sides of the non-rebreathing bag from damaging the oxygen-sensitive surface of the cornea of the eye. The patient is exercised until the target aerobic heart rate is achieved and maintained for 15 minutes followed by a 3- to 5-minute cool down period. At our facility, continuous treadmill electrocardiogram (ECG) monitoring is performed to assess changes in cardiac rhythm and ischemic status.

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Table 1

√	Pill#	Supplement
❑	___	Arginine 500 mg, vasodilator via nitric oxide
❑	___	Coenzyme Q10 100 mg, antioxidant
❑	___	Dimethylglycine, 125 mg, oxygenator, glutathione precursor
❑	___	Grapeseed extract, slow release, platelet aggregation inhibitor, improves small vessel circulation
❑	___	G-strophanthin, alkalinizing to myocardium, 6 mg
❑	___	L-glutamine, 500 mg, glutathione precursor
❑	___	Magnesium glycinate, 120 mg, vasodilator
❑	___	Magnesium orotate, 100 mg
❑	___	NAC (N-acetylcysteine), 600 mg, quenches nitric oxide as glutathione precursor
❑	___	Niacin 250 mg, immediate release, vasodilator
❑	___	Niacin 500 mg, slow release, vasodilator
❑	___	Oxy Quench (antioxidant), 1–2
❑	___	*Panax ginseng*, 50 mg
❑	___	Resveratrol, 100 mg, slow release
❑	___	Rx, dipyridamol 25, 50, 75 mg Rx 50 mg/70 kg BW, platelet aggregation inhibitor, dilates coronary arteries
❑	___	Rx, Hydralazine, peripheral vasodilator, 10 mg (contraindicated in CAD)
❑	___	Vitamin B complex, active form, sublingual, 1–2, cellular energy
❑	___	Vitamin B 1 (thiamin), 30 mg, swallow, cellular energy
❑	___	Vitamin B 15, pangamic acid, 30 mg
❑	___	Vitamin C, 1000 mg, 1-2-3, swallow, antioxidant
❑	___	Vitamin E 1:1, high gamma-tocopherol, antioxidant vasodilation protection

The clinician chooses one of the three between L-arginine, dipyridamol, or Hydrazine as best vasodilator at the safest dose given the patient's resting blood pressure. Vasodilators may be contraindicated in cancer patients. Beware of the agonistic effects of adding magnesium and niacin with other vasodilators. When giving L-arginine or nitroglycerin directly, add vitamin E 1:1 high gamma-tocopherol and/or CoQ10 and consider adding the glutathione precursors of dimethylglycine, glutamine, and cysteine or NAC. Glutathione, gamma-tocopherol, and CoQ10 quench the adverse effects of nitric oxide.

Oxygen Multistep Therapy

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Case Study: Postsurgical Bicuspid Aortic Valve Replacement

This therapy is particularly useful as a replacement for, or an addition to, postsurgical cardiac rehabilitation therapy. As with conventional cardiac rehabilitation, OMST further maximizes chances of collateral small vessel formation with increasing load to safe maximum tolerance. Below we discuss the case of a 68-year-old female who performed a total of six OMST treatments at CNM with favorable results.

M. T. is a delightful person who first presented to our clinic 4 months after surgery for bicuspid aortic valve replacement. Her main postoperative complaints were of fatigue, insomnia, and digestive distress. She had no history of concomitant hypertension, congestive heart failure, chest pain, or stroke. Her medications included metoprolol, a selective beta-1 receptor blocker, which appeared to be contributing to her fatigue and lethargy. We explained the necessity of continuing this medication for at least 9 months after surgery to minimize the load on the heart during the cardiac remodeling phase. It was at this time that we scheduled her initial ETT.

The patient's resting electrocardiogram revealed a right bundle branch block, but was otherwise normal. She had taken metoprolol 2 hours before the procedure. Her target aerobic heart rate was calculated to range from 103 to 122 bpm at 50% to 70% of her maximum heart rate. The patient was exercised for 5 minutes until the target aerobic heart rate of 103 bpm was achieved; 120 bpm was achieved at 10 minutes. Although M. T. appeared fatigued, she completed a satisfactory pretreatment ETT, and we subsequently prescribed a once weekly series of three OMST treatments. She was instructed to hold her morning dose of Metoprolol before exercise sessions in order to achieve an increased target heart rate of 115 to 126 bpm at 60% to 70% of her maximum.

Table 2

	Dysrhythmia During Exercise	Dysrhythmia During Recovery
Pre-Tx ETT	None*	None*
OMST #1	None	3 isolated PVCs 5 bigeminal paired PVCs
OMST #2	4 isolated PVCs during stage II 1 isolated PVC at stage III 4 isolated PVCs at stage IV	2 isolated PVCs
OMST #3	7 isolated PVCs during stage III 1 isolated PVC at stage IV	7 isolated PVCs

* beta blocker was likely controlling heart rate and rhythm

Table 3

	Dysrhythmia During Exercise	Dysrhythmia During Recovery
OMST #4	None	None
OMST #5	1 isolated PVC during stage II	2 isolated PVC 1 bigeminal paired PVC
OMST #6	None	3 isolated PVC
Post-Tx ETT	None	1 isolated PVC

After the first three treatments, the patient reported an increase in energy and improved exercise tolerance. Frequent and intermittent isolated premature ventricular contractions (PVCs) and occasional bigeminal PVCs were observed during exercise and recovery (see Table 2). These beats were not associated with symptoms and resolved after 10 minutes of rest. Our impression was that she might benefit from further oxygen therapy, and we recommended a series of three additional OMST treatments. We also increased her exercise intensity in order to achieve a heart rate of 125 to 134 bpm, 70% to 80% of her maximum heart rate.

M. T. noted a significant increase in energy and well-being after completion of the second three treatments, and premature beats were reduced (see Table 3). She denied any symptoms of palpitations or shortness of breath with exertion. Her sleep had significantly improved and most of her initial presenting complaints had resolved. Overall, her outward demeanor and vigor were noticeably enhanced. She made an appointment with her MD cardiologist, who, after reviewing an echocardiogram that showed good left ventricular function, agreed to let her wean off metoprolol with close monitoring of blood pressure.

The patient was instructed to continue with home exercise at a target heart rate of 130 bpm for 30 minutes every other day. In addition to this we prescribed a customized nutrient packet for her to take before exercise to encourage oxygen utilization that included the following:

- 4 capsules arginine (500 mg each)
- CoQ10 100 mg
- dimethylglycine sublingual 250mg
- magnesium glycinate 120 mg
- active B complex, 1 tab sublingual
- vitamin E 1:1 (gamma-tocopherol), 400 IU

Oxygen Multistep Therapy

Clinical Application and Implications

The effects of OMST are promising and potentially far reaching in the management of a wide range of conditions associated with impaired oxygen uptake and cellular utilization. It is clear that more clinical research and case studies should be conducted in this regard to further substantiate efficacy. This protocol would also lend itself to a double-blinded prospective study. We are continuing to pursue clinical application of this therapy, and encourage physicians interested in promoting optimal health in their patients to consider doing the same.

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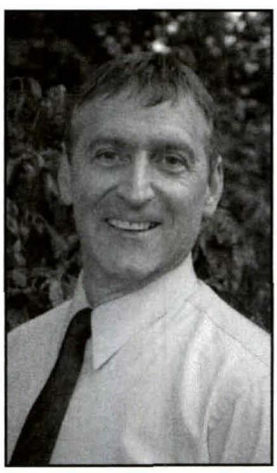

Martin Milner, ND, has been in private practice since 1983 and is the medical director of the Center for Natural Medicine Inc. CNM functions as an integrated group medical practice, a naturopathic patient-centered primary care home (PCPCH), and as a teaching clinic of National College of Natural Medicine (NCNM). CNM is also active in research with both Helfgott Research Institute and Naturopathic Education and Research Consortium (NERC). Dr. Milner is the professor of cardiovascular and pulmonary medicine at NCNM and has been since 1987. He is the 2013 recipient of the prestigious NCNM-OANP Living Legend Award. He continues to supervise and mentor 48 ND student interns per year in the Heart & Lung Wellness Program, which he has maintained since 1999. He trains two ND residents each year, one who assists him in the Heart & Lung Wellness Program, currently Dr. Nathaniel Bingham, and one in his private practice, currently Dr. Janna Redding. Dr. Milner is actively pursuing the creation of the first board certification program for NDs in naturopathic cardiology with Dr. Jeremy Mikolai (his former chief resident, current coattending physician in the H&L program, and current first Integrated Cardiovascular Medicine Fellow at NERC). In December 2013, NCNM announced the formation of the first in the world Center of Excellence in Naturopathic Cardiovascular Medicine, a collaborative alliance between the Center for Natural Medicine's Heart & Lung Wellness program, NCNM, and the Helfgott Research Institute at NCNM.

Janna Redding, ND, is the Center for Natural Medicine's resident physician under the mentorship of Dr. Martin Milner. She earned her BS degree in general science with an option in physical therapy and graduated magna cum laude from Oregon State University in 2006. Her interest in health care from a holistic perspective led her to the National College of Natural Medicine, where she completed her naturopathic doctorate in 2012. While at NCNM, Dr. Redding completed two specialized rotations with Dr. Milner, focusing on cardiopulmonary (heart and lung) and endocrine (hormone) conditions. During her medical training, she also developed an interest and gained experience in treating neurotransmitter imbalances as related to immune and endocrine function. She is invested in individualized care, and committed to promoting and maintaining overall wellness in her patients.

No Disease – Ever! Unlocking The Power of Oxygen

by Frank Shallenberger, MD, HMD

I trust that the unassuming title of this paper caught your eye. "No Disease – Ever!" What the heck is that supposed to mean? Has he got some kind of special supplement that I don't know about? Or is he just shooting off his mouth? Sorry; but to borrow a line from Nancy Pelosi, you'll have to read the article to find out. But here's something that you already know. There are tens of thousands of people every year who live out long lives and never get a chronic disease. So how do they do that? I think I know. And I'll tell you how.

But first, let me digress to an equally important topic: money. Do you have any idea how much money it costs people to be sick? I hadn't a clue until a remarkable report came out in the *Boston Globe* titled "Retired Couples May Need $240,000 for Health Care." It was written by Mark Jewell and published by the Associated Press on May 9, 2012.

The author used data compiled by Fidelity Investments that determined what the average out-of-pocket costs for medical expenses would be for a couple who were both 65 years old if they lived to their life expectancy. For men that is 82 years old, for women 85. That number came out to be a whopping $240,000! That includes the cost of Medicare premiums for our couple, which amounts to about $93,000 for both Medicare Part A and Part B. The net difference comes to $147,000! That's $147,000 extra money in that couple's pocket for not getting sick.

But that's not all. $240,000 is just the average number. 50% of those people will be paying more than that. Some will be paying twice that. And it gets worse. These costs don't even include dental expenses or long-term care, which could easily add up to thousands more.

The way I figure it is, if I can only stay healthy until I'm 82, it will be like someone writing a check out to me for $74,000 or more. Wow, that's something this man can relate to – feeling and functioning at a high level, being medication free, and being $74,000-plus richer. So with that in mind, I guess I shouldn't complain too much about paying for that gym membership, all the tests, and all those supplements. But can it really be done? Yes, it can!

Right now there are an estimated 80,000 people in the US who are more than 100 years old. Virtually all of these people have been completely free of disease all their lives. I have quite few patients in their mid- to late 80s who are free of disease, fully functional, and on no medications.

Redd Fox once said, "Imaging all those health nuts lying in hospitals dying of nothing." Obviously, the healthier you live your life, the less the chance of getting a disease. But is there a central foundation to this story? Is there a process that goes on in the body that is at the very core of what makes us more or less vulnerable to disease? The answer is yes. So I'm going to ask you discover it yourself right now. Simply hold your breath for the next 60 seconds, and then read on.

What happened? Did you feel good? Did you become weak, dizzy, anxious? Did your heart pound? Did you feel like you might be dying? Did your blood pressure go up? Clearly there is absolutely nothing as critical to our health as oxygen metabolism. And yet as critical as it is, virtually every doctor you will see in these United States will never once test it in his or her patients. Why? Because we were taught in school that as long as you are breathing, have normal lungs, and have a normal oxygen blood level, your oxygen metabolism must be optimal. But here's the thing: That is just not correct.

There is much more to any nutrient than simply how much you take in. The other aspect is how efficiently you use the nutrient. You can take in vitamin B6 all day long, but if you can't efficiently use it, you are going to be mostly wasting it. This is also true of oxygen. You can be breathing good air and have normal levels of oxygen in your blood, but that in no way means you are using it efficiently.

Oxygen utilization is the term that I coined to refer to how efficiently your body uses the oxygen that you take in. And now we are getting down to business. *Because your oxygen*

utilization is the single most important predictor of your risk for degenerative disease and premature aging. It's not what you take in that determines your health – it's what you use. How do I know? Because for the past 12 years, I have been measuring the oxygen utilization on each and every one of my patients whether they are sick or well. And after looking at literally thousands of patients, I noticed an absolutely stunning statistic.

Every single patient who had cancer or any other chronic disease had a very significant decrease in his/her oxygen utilization. 100% of them! That goes for an otherwise "healthy" woman with a cancerous breast lump. It also goes for the "healthy" man on meds for hypertension. Combine that observation with this one. Over the same 12 years, I never once saw anyone with healthy oxygen utilization come down with cancer, a heart attack, an autoimmune disease, or any other chronic disease. Not one. As long as their oxygen utilization was in the pink, 100% of them appeared to be completely invulnerable to illness.

What would be the reasons for these incredible observations? I can think of two. The first is free radical production. All doctors agree that free radical excess is at the heart of aging and chronic disease. But what determines your level of free radical production? You guessed it – it's the efficiency of your oxygen metabolism. The greater your oxygen utilization, the less free radicals you produce. The worse your oxygen utilization, the more you produce. It's that simple. But there's another reason.

Oxygen utilization is the most global and sensitive marker for health that there is. That's because, as important as it is, the process is very vulnerable. Almost anything will disrupt it. So when someone's oxygen utilization is optimal, it means that virtually everything in that person's lifestyle and environment is matching up perfectly with their genetics. No wonder they don't get sick.

But is there any other evidence that decreased oxygen utilization is the root of disease? Yes, lots of it.

Oxygen is metabolized in little bubbles in each cell called mitochondria. Remarkably, in a truly healthy person, mitochondria make up almost 50% of the entire mass of a cell. That's how important they are. Roughly 10% of your entire body weight is mitochondria. And here's the important part. Your oxygen utilization is a direct indicator of how well your mitochondria are functioning.

If you search the US National Library of Medicine website PubMed for "mitochondria and aging," you will find 6297 papers linking aging to decreased mitochondrial function. If you search for "mitochondria and disease," you will find 16,318 citations. And if you search for mitochondrial function and any particular degenerative disease that you can think of, you will find hundreds of references for each disease. All of these papers directly tie oxygen utilization to both aging and disease.

Today we are still led to believe that as long as we feel good and our physical examinations and routine blood tests are normal, then we are healthy. But this is just not true. There are many people out there who meet all these criteria and yet have very poor oxygen utilization. In fact, we know that long before people actually get sick, they have been on the road to disease for years. This road is called decreased oxygen utilization.

So, how can oxygen utilization be measured? Here's how I do it. I use an FDA-approved pulmonary gas analyzer. This equipment can measure how much oxygen disappears into your body; in other words, how much oxygen you are using. I make that measurement while you are resting quietly in a recliner. Then I put you on a bicycle and I measure how much oxygen you are using during various levels of exertion. But at the same time that the analyzer is measuring how much oxygen you are using, it is also measuring how much carbon dioxide you are making. Why is that?

It's because as your body uses oxygen it generates carbon dioxide as a byproduct. Don't tell Al Gore, but every breath he takes, he is contributing to the carbon dioxide in our atmosphere. But here's the thing. When you are using oxygen efficiently, you generate less carbon dioxide. And when your use of oxygen is inefficient, you make more carbon dioxide. So the efficiency at which a person uses oxygen depends on their ratio of oxygen consumed to carbon dioxide produced at specific levels of exertion.

When I determine how efficiently my patient is using oxygen, I compare it with what would be typical for a person who is healthy and young. I call the result their energy quotient, or EQ. If their EQ is 100%, that means that they are using oxygen as efficiently as a healthy young person. That's the goal. The higher your EQ is, the less likely that you are ever going to get a disease. As I mentioned above, I have never seen anyone with an EQ over 100% come down with any disease, period. So now let me show you how oxygen utilization testing works in the real world with a couple of real cases.

The first patient's name is Frank. Frank is 67 years old. He started having his EQ measured back when he was 55. Each year was the same; his EQ was a remarkable 140–160. This means that his oxygen utilization was 40% to 60% better than the average young man's. There was no way that Frank was going to get sick with any disease with an EQ that good.

But starting somewhere in his early 60s, Frank started to get overconfident. He slacked off on his exercise schedule. His life became more complicated, and he became more stressed and less fit. Oh yes, and by the way, he got 5 years older. Sound familiar? So what happened?

Frank's EQ started to drop every year. When he was 66, it had fallen

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to 104. That's certainly respectable for a 66-year-old, but not up to his former glory. And then came the big tap on the shoulder. Just a few months ago, it dropped to 72! Frank had lost his invulnerable status. And he was starting to wonder if he was going to be able to collect that $75,000 that Fidelity Investments had promised him. And here's the punch line. Frank wasn't just any patient. Frank is me!

So here I am at age 67, feeling and functioning great at every level, but knowing that unless things change, I might not be that way for long. Without that wake-up call, I would never have guessed that I was going downhill. So seven months ago, I started to clean up my lifestyle. I got more consistent with my supplements and exercise, and I decreased my stress load. Last month, my EQ had come up to 87. Still not there, but at least I'm on my way. Here's a different kind of case.

Just yesterday I had a 59-year-man named Chris come in for his annual oxygen utilization testing. Normally Chris tests extremely well. But 14 months ago he had a hip replacement and the prosthesis was releasing cobalt. For the past seven months his blood levels of cobalt were five times the upper limit of normal. He felt great but was concerned that the cobalt might be interfering with his health. It wasn't. His EQ was an astounding 160%, the best it had ever been. This is great information for Chris, because it assures him that even with these elevated levels of cobalt, he is still in good health and at no risk for disease. Of course we will continue to test him every year to make sure he stays that way.

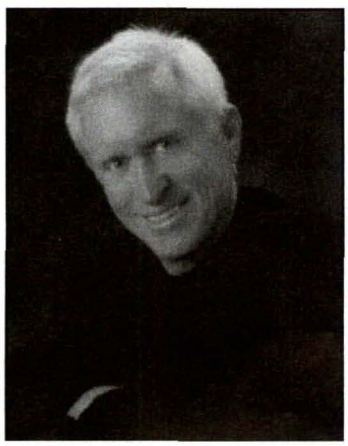
Even from just these two examples, you can see why the first thing I measure in my patients is their oxygen utilization. I think it is the most important test anyone can have. Most of the time, especially in the over-40 crowd, the results indicate that help is needed. And fortunately, most of the time it improves.

What are the key issues that turn up for most people? They're things like stress, carbohydrate excess, nutrient deficiencies, hormonal deficiencies, inflammation, heavy metal toxicity, pharmaceutical toxicity, decreased circulation, chronic infections (think intestinal, dental, and sinus here), and inadequate sleep. So these are the things we work with. And by retesting their EQ at regular intervals, we can find out if what we are doing is actually working.

And here's the good news. This testing system is now commercially available. So the days when doctors treat their patients without ever having a clue as to what their oxygen utilization is are now officially over. The name of the testing process is Bio-Energy Testing. You can find the closest doctor offering the test in the Bio-Energy Testing Centers list found at www.bioenergytesting.com. If you go to the video page on my website, www.antiagingmedicine.com, you can access for no charge several lectures that I have given on oxygen utilization and health.

By the way, there is a ton of other important information you can get from the Bio-Energy testing process, including metabolic rate, fat burning rate, resting fat metabolism, heart function, lung function, functional strength, exercise data, and diet data. Your doctor can use all of that information to help improve your EQ if it needs help.

Try to make it a point this year to find out how you are doing. If your oxygen utilization is great, then you know that you are on the right path. If not, at least you are forewarned, and can make the appropriate changes before it is too late.



Dr. Shallenberger is a five-time grandfather and four-time father. He has been practicing alternative/integrative medicine since 1978. He is the president of the American Academy of Ozonotherapy and vice president of the Society of Orthomolecular Health Medicine. Dr. Shallenberger has revolutionized the practice of anti-aging and preventive medicine by developing a method to measure mitochondrial function and oxygen utilization. He has written two popular books describing this method, *The Type 2 Diabetes Breakthrough* and *Bursting With Energy*, and has authored numerous papers in the international peer reviewed literature on ozone therapy and oxygen utilization. He is also the editor of *Real Cures* alternative medicine newsletter. Dr. Shallenberger has just been elected to serve as a charter member of the International Scientific Committee on Ozone Therapy. He is the developer of Prolozone, an injection technique that has been shown to regenerate damaged joints, herniated discs, and degenerated joints, tendons, and soft tissues.

Financial Disclosure

Dr. Shallenberger is financially associated with Bio-Energy Testing LLC and holds a patent on the Bio-Energy Testing process.

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What Causes Heart Attacks

by Dr. Thomas Cowan

In this article, I lay out the case that the spectrum of heart disease that includes angina, unstable angina, and myocardial infarction (heart attack) is better understood from the perspective of events happening in the myocardium (heart) as opposed to events in the coronary arteries (the arteries that supply the heart). As we all know, the conventional view of the cause of heart disease is that the central events occur in the arteries. In this article, I will go into more detail about why the conventional theory is largely misleading, and then I will describe the precise and well-documented events that do lead to heart attacks.

This new understanding is crucial because, as the past 50 or so years have shown, pursuing the coronary-artery theory has cost this nation billions of dollars in surgical costs – most of which are unnecessary – and billions in medications that cause as much harm as any benefits, and has led many people to adopt a low-fat diet and which only worsens the problem. In contrast, by understanding the real pathophysiological events behind the evolution of MIs, we will be led to a proper "Nourishing Traditions"-style diet, the use of the safe and inexpensive medicine g-strophanthin, and most important, we will be forced to look at how heart disease is a true manifestation of the cost of modern life to human health. To overcome the epidemic of heart disease, we need a new medical paradigm, a new economic system, and a new ecological consciousness; in short, a new way of life. The coronary theory misses all of this, just as it misinterprets the actual pathological events.

In writing this article, I am indebted to the work of Dr. Knut Sroka and his website www.heartattacknew.com. For all who are interested in this important subject, it is advised to read the entire website and watch the video on the website. For health professionals and researchers, your understanding of this subject is incomplete without reading and studying two items found in the print version of the website: *The Etiopathogenesis of Coronary Heart Disease: A Heretical Theory Based on Morphology*, by G. Baroldi, and "On the Genesis of Myocardial Ischemia," by Sroka.

Rebuttal of the Conventional Theory

Until recently, it was thought that most MIs were caused by progressive blockage created by plaque buildup in the major arteries leading to the heart (there are four major coronary arteries). The plaque was thought to be cholesterol buildup in the arterial lumen (inside of the vessel), which eventually cut off blood supply to a certain area of the heart, resulting in oxygen deficiency in that area, causing first pain (angina), then progressing to ischemia (heart attack). The simple solution was to unblock the stenosis (blockage) with either an angioplasty or stent, or, if that was not possible, to bypass the area with coronary bypass grafting (CABG). Simple problem, simple solution.

However, problems became apparent through a number of avenues. First, a story related by a cardiologist at a Northern California heart symposium, at which I was a speaker, points to the first problem. He told us that during his residency he was part of a trial conducted in rural Alabama with black men. In this trial, angiograms (injections of dye into the coronary arteries to detect blockages) were done on all the men presenting with chest pains. For the ones who had a single artery blocked, no treatment was prescribed, and the researchers predicted in their notes which part of the heart would have a subsequent heart attack if one occurred. Of course, they all predicted that it would be in the part of the heart supplied by the blocked coronary artery. Then they waited.

Eventually, many of the men did return and did have MIs, but to the researchers' surprise, less than 10% had a heart attack in the area of the heart supplied by the original blocked artery.

Second, a large study conducted in 2003 by the Mayo Clinic on the efficacy of bypasses, stents, and angioplasty concluded that:

a. bypass surgery relieves symptoms (chest pain);
b. bypass surgery does not prevent further heart attacks;
c. only high-risk patients, those whose lives are in acute danger, benefit from bypass surgery with regard to a better chance of survival.

In other words, the gold standard for treating arterial blockages has, at best, only minimal benefits. If you watch the video on the heartattacknew.com website and go to the FAQ called "The Riddle's

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Solution," it becomes clear why this is so. Large, stable blockages – those over 90% – are in almost 100% of the cases completely compensated by collateral blood vessels. In fact, the view that the heart gets its blood only from the four major vessels is itself false. Starting soon after birth, the normal heart develops an extensive network of small blood vessels called collateral vessels, which eventually compensate for the interruption of flow in any one (or more) of the major vessels.

As Sroka correctly points out in the video, coronary angiogram – by failing to show the collateral circulation, and by creating spasms in the coronary arteries through the injection of heavy dye under high pressure – is notoriously inaccurate at assessing the amount of stenosis in the vessels as well as the true blood flow in the heart. To this day, most of the bypasses, stents, and angioplasties are done on minimally symptomatic patients who show a greater than 90% blockage in one or more coronary arteries. These arteries are almost always fully collateralized; the surgery does not restore blood flow because the body had already done its own bypass. Ask yourself: If it were true that an artery more than 90% blocked had no collateral circulation, how would that person still be alive? And does it really make sense that the eventual MI is caused when the stenosis goes from 93% to 98%? This is an insignificant difference and is completely nonsensical. Yet this is what most of the procedures are meant to accomplish, to unblock the stenosis, which, as the video shows, actually has no blood-flow repercussions. It is no wonder that in study after study these procedures fail to provide any significant benefit to patients.

For these reasons, the stable-plaque model is being abandoned by conventional cardiology, in favor of a different model for the etiology of MIs, which, as it turns out, is almost equally invalid.

Meet the Unstable Plaque

So, we all agree that the entire focus of cardiology – the stable, progressing, calcified plaque, the thing that we bypassed and stented for years, the thing that we do CT scans of your arteries for, the thing that we told you is from cholesterol buildup in your arteries, the thing that "alternative cardiology," such as the Ornish program, focused on – actually is not so important in the etiology of heart attacks. Don't worry, though. We know that the focus of the problem *must* be the arteries, or so conventional thinking goes. Therefore, enter the unstable, or friable, plaque. This insidious fellow doesn't actually create a large blockage; rather, it's a soft, "foamy" plaque that under certain situations (we don't know which situations) rapidly evolves and abruptly closes off the involved artery, creating a downstream oxygen deficit, followed by angina, then ischemia. These soft plaques are thought to be a combination of inflammatory "buildup" and LDL, the exact two things targeted by statin drugs. Therefore, the thinking goes, because this type of plaque can build up in anyone's arteries, at any time, everyone should be on statin drugs to prevent heart attacks. (Some people even advocate putting therapeutic doses of statins in municipal water supplies.) Angiogram studies have been presented to show the evolution of these unstable plaques as proof that they are the true cause of the majority of MIs.

As I will show in the next section, acute thrombosis does happen in patients having MIs, but it is a *consequence*, not the cause, of the MI. But how often does it actually happen? Let's look at pathology studies, which are the only accurate way to determine what actually happened, as opposed to angiograms, which are misleading and create many artifacts. The first major autopsy/pathology study of people who died of MIs was done in Heidelberg in the 1970s.[1] The conclusion was that thrombosis sufficient to cause the MI was found in only 20% of cases. Baroldi, in the largest such study ever done, found sufficient thrombosis in 41% of cases.[2] He also found that the larger the area of the MI, the more often a stenosis was present, and the longer the time between MI and death, the higher the percentage of stenosis. These two facts allow some researchers to "cherry-pick" the numbers and make the stenosis rate high, as they choose to study only those with large MIs and who live the longest after the MI event. Later in this article, I will explain how the stenosis comes about as a consequence of the MI.

Another observation that casts doubt on the relevance of the coronary artery theory of MI has to do with the proposed mechanism of how thrombosed arteries cause ischemia, which is by cutting off the blood supply and thereby the oxygen to the tissues. The reality is that when careful measurements are done assessing the pO2 (oxygen level) of the myocardial cells during an MI, to the huge surprise of many, there is no oxygen deficit ever shown in an evolving MI.[3] The pO2 levels do not change at all throughout the entire event. I will come back to this later when I describe what does change in every evolving MI ever studied. Again, the question must be asked, if this theory is predicated on the lowering of the pO2 in the myocardial cells, and in fact the pO2 doesn't change, then exactly what did happen?

The conclusion is that thrombosis associated with MI is a real phenomenon, but in no pathological study has it been found in more than 50% of deaths, which raises the question, why did the other 50% even have an MI? Second, it's clear from all pathology studies that thrombosis of significant degrees evolve *after* the MI occurs, again leading to the question of what caused the MI in the first place. The fact that thrombosis does occur also

explains why emergency procedures (remember, the only patients who benefit from bypass and stents are the most critical, acute patients) can be helpful immediately post-MI to restore flow in those patients who do not have adequate collateral circulation to that part of their heart. So again, all the existing theories as to the relevance of the coronary arteries in the evolution of the MI are fraught with inconsistencies.

If this is so, what then does cause MIs?

The Etiology of Myocardial Ischemia

Any accurate theory of the cause of myocardial ischemia must account for the risk factors most associated with heart disease. These are: being male, having diabetes, smoking cigarettes, and experiencing chronic psychological/emotional stress. Interestingly, none of these risk factors directly link to pathology of the coronary arteries. Diabetes and cigarette use cause disease in the capillaries, not the large vessels, and stress has no direct effect on coronary arteries that we know of.

In addition, during the past five decades or so, the four main medicines of modern cardiology – B-blockers, nitrates, aspirin, and statin drugs – all have some benefits for heart patients (albeit all with serious drawbacks as well), which must be addressed in any comprehensive theory of myocardial ischemia, which I will attempt to do here.

The real revolution to come in the prevention and treatment of heart disease has been inaugurated through our understanding of the role of the autonomic nervous system in the genesis of ischemia and its measurement through the tool of heart-rate variability. First, some brief background. We have two distinct nervous systems. The first, the central nervous system, controls conscious functions such as muscle and nerve function. The second nervous system is called the autonomic (or unconscious) nervous system (ANS), which controls the function of our internal organs. The autonomic nervous system is divided into two branches, which in health are always in a balanced but ready state. The sympathetic, or fight-or-flight, system is centered in our adrenal medulla and uses the chemical adrenaline to tell our bodies that danger is afoot, it's time to run. It does so by activating a series of biochemical responses, the center of which are the glycolytic pathways that accelerate the breakdown of glucose to be used as quick energy so that we can make our escape.

In contrast, the parasympathetic branch, centered in the adrenal cortex, is the rest-and-digest arm of the autonomic nervous system. The particular nerve of the parasympathetic chain that innervates the heart is called the vagus nerve. It slows and relaxes the heart whereas the sympathetic branch accelerates and constricts the heart. It is the imbalance of these two branches that is responsible for the vast majority of heart disease.

Using heart-rate variability monitoring, which gives a real-time, accurate depiction of the status of these two branches of the ANS, it has been shown in four studies that patients with ischemic heart disease have, on average, a reduction of parasympathetic activity of more than a third. Typically, the worse the ischemia, the lower the parasympathetic activity (5/134). Furthermore, about 80% of ischemic events have been shown to be preceded by significant, often drastic, reductions in parasympathetic activity related to physical activity, emotional upset, or other causes.[6] This finding contrasts with others that show that people who have normal parasympathetic activity, then have an abrupt increase in sympathetic activity (physical activity, or often an emotional shock), never suffer from ischemia. In other words, without a preceding decrease in parasympathetic activity, activation of the sympathetic nervous system does not lead to MI.[7] Presumably, we are meant to have times of excess sympathetic activity; that is normal life. What's dangerous to our health is the ongoing, persistent decrease in our parasympathetic, or life-restoring, activity. This decrease in parasympathetic activity is mediated by the three chemical transmitters of the parasympathetic nervous system: acetylcholine, NO, and cGMP. This is where it becomes fascinating, for it has been shown that women have stronger vagal activity than men, probably accounting for the sex difference in the incidence of MI.[8] Hypertension causes a decrease in vagal activity, smoking causes a decrease in vagal activity, diabetes causes a decrease in vagal activity, and physical and emotional stress also causes a decrease in parasympathetic activity.[9–12] So all the significant risk factors have been shown to downregulate the activity of the regenerative nervous system in the heart.

On the other hand, the main drugs used in cardiology – nitrates – stimulate NO (nitrous oxide) production, which upregulates the parasympathetic nervous system. Aspirin and statin drugs also stimulate the production of ACH and NO, two of the principal mediators of the parasympathetic nervous system (until they cause a rebound decrease in these substances, which then makes the parasympathetic activity even worse). Finally, B blockers are called B-blockers because they block the activity of the sympathetic nervous system. To summarize, the risk factors and interventions that have actually been borne out through time all help balance the ANS. Whatever their effect on plaque and stenosis development is of minor relevance.

So, what is the sequence of events that leads to an MI?

First, and in the vast majority of cases the pathology will not proceed unless this condition is met, there is a decreased tonic activity of the parasympathetic nervous system. Then comes an increase in the sympathetic

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nervous system activity, usually a physical or emotional stressor, which raises adrenaline production, which directs the myocardial cells to break down glucose using aerobic glycolysis (remember, no change in blood flow as measured by the pO2 in the cells has occurred). This development redirects the metabolism of the heart away from its preferred and most efficient fuel source, which is ketones and fatty acids. This explains why heart patients often feel tired before their events. This also explains why a high-fat, low-glucose diet is crucial for heart health. As a result of the sympathetic increase and resulting glycolysis, a dramatic increase in lactic acid production occurs in the myocardial cells. This happens in virtually 100% of MIs, with no coronary artery mechanism required.[13,14] As a result of the increase in lactic acid in the myocardial cells, a localized acidosis occurs. This acidosis causes the calcium to be unable to enter the cells, making the cells less able to contract.[15] This inability to contract causes localized edema, dysfunction of the walls of the heart (called hypokinesis, the hallmark of ischemic disease as seen on stress echoes and nuclear thallium stress tests), and eventually necrosis of the tissue, which we call an MI. The localized tissue edema also alters the hemodynamics of the arteries embedded in that section of the heart, causing the sheer pressure that ruptures the unstable plaques, which further blocks the artery and worsens the hemodynamics in that area of the heart. Only this explanation tells us why plaques rupture, what their role in the MI process is, and when and how they should be addressed; that is, only in the most critical, acute situations. Only this explanation accounts for all the observable phenomena associated with heart disease. The true origin of heart disease could not be more clear.

The final question is, why is this understanding of heart disease relevant, besides being of academic interest? The first and obvious answer is that if you don't know the cause, you can't find the solution. The solution is to protect our parasympathetic activity, use medicines that support it, and nourish the heart with what it needs. Nourishing our parasympathetic nervous system is basically the same as dismantling a way of life for which humans are ill suited. This way of life, in my view, is otherwise known as industrial civilization. The known things that nourish the parasympathetic nervous system are contact with nature, loving relations, trust, economic security (a hallmark of indigenous peoples the world over), and sex – in a sense, a whole new world.

The medicine that supports all aspects of the parasympathetic nervous system is a medicine from the strophanthus plant called ouabain, or g-strophanthin. G-strophanthin is an endogenous hormone made in the adrenal cortex from cholesterol, whose production is inhibited by statin drugs, that does two things that are crucial for heart health and are done by no other medicine. First, it stimulates the production and liberation of ACH, the main neurotransmitter of the parasympathetic nervous system. Second, and crucially, it converts lactic acid – the main metabolic poison in this process – into pyruvate, one of the main and preferred fuels of the myocardial cells. In other words, it converts a "poison" into a nutrient.

Perhaps this "magic" is why Chinese medicine practitioners say that the kidneys (i.e., adrenals, where ouabain is made) nourish the heart. In my years of using ouabain in my practice, I have not had a single patient who had an MI while taking it. It is truly the gift to the heart.

Finally, this understanding of heart disease leads us to the correct diet, one that is loaded with healthful fats and fat-soluble nutrients, and is low in the processed carbohydrates and sugars that are the hallmark of industrial, civilized life.

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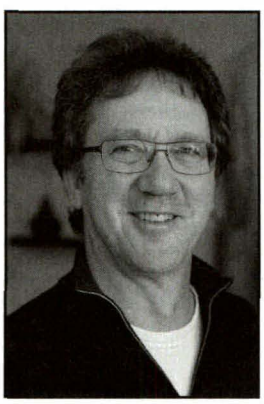

Dr. Tom Cowan discovered the work of the two men who would have the most influence on his career while teaching gardening as a Peace Corps volunteer in Swaziland, South Africa. He read *Nutrition and Physical Degeneration*, by Weston Price, and a fellow volunteer explained the arcane principles of Rudolf Steiner's biodynamic agriculture. These events inspired him to pursue a medical degree. Tom graduated from Michigan State University College of Human Medicine in 1984. After his residency in family practice at Johnson City Hospital in Johnson City, New York, he set up an anthroposophical medical practice in Peterborough, New Hampshire. Dr. Cowan relocated to San Francisco in 2003.

Dr. Cowan has served as vice president of the Physicians Association for Anthroposophical Medicine and is a founding board member of the Weston A. Price Foundation. During his career he has studied and written about many subjects in medicine. These include nutrition, homeopathy, anthroposophical medicine, and herbal medicine. He is the principal author of the book *The Fourfold Path to Healing*, which was published in 2004 by New Trends Publishing, and is the coauthor of *The Nourishing Traditions Book of Baby and Child Care*, published in 2013. He writes the "Ask the Doctor" column in *Wise Traditions in Food, Farming and the Healing Arts*, the foundation's quarterly magazine, and has lectured throughout the US and Canada. He has three grown children and currently practices medicine in San Francisco, where he resides with his wife, Lynda Smith Cowan. Dr. Cowan sees patients at his office in San Francisco, does long-distance consults by telephone, and is accepting new patients. He also gives lectures and presentations.

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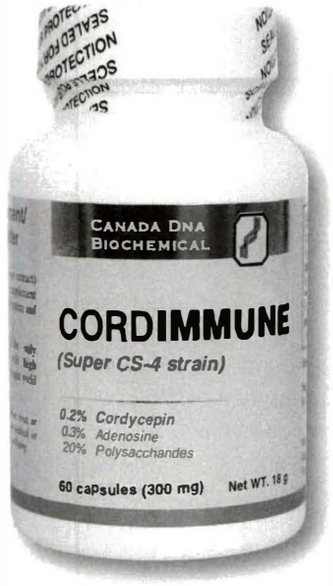

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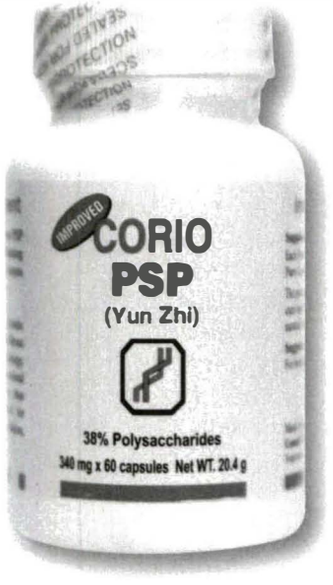

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Seasonal Allergies and Asthma: Removing Total Burden For Powerful Symptom Relief and Whole Body Wellness

by Chris D. Meletis, ND, and Kimberly Wilkes

Seasonal allergies and asthma are two respiratory-related conditions often "joined at the hip." A study published in April 2013 found that 75% of asthmatic adults aged 20 to 40 years old, and 65% of asthmatic adults aged 55 years and older, suffer from at least one allergy.[1]

Another study, presented in November 2013 at the American College of Allergy, Asthma and Immunology's (ACAAI) Annual Scientific Meeting, found that the number of people with asthma who also have a cat allergy more than doubled over 18 years, from 1976 to 1994. The same study found that people who have asthma are more likely to be allergic to environmental allergens such as ragweed, ryegrass, and *Alternaria* fungus.[2]

Clemens von Pirquet coined the term *allergy* in 1906 to describe the tendency of some individuals to develop signs and symptoms of reactivity – otherwise known as hypersensitivity reactions – when exposed to certain substances.These hypersensitivity reactions involve an abnormal adaptive immune response aimed at what should be harmless, noninfectious environmental substances (allergens).[3]

Asthma is an inflammatory disease of the lower respiratory tract characterized by intermittent constriction of the bronchial airways. Asthma attacks can cause symptoms ranging in severity from mild to life-threatening. These symptoms include wheezing, breathlessness, chest tightness, and coughing.[4]

According to the Centers for Disease Control, by 2004, 1 in every 15 residents in the US – 20 million people – had asthma, with half of those cases attributed to allergic asthma.[5] Currently, more than 25 million people are known to suffer from the disease.[6]

This article will discuss the connections between asthma, allergy, and other diseases, and why a person must reduce the total burden before a supplement regimen can be effective.

Two Diseases Linked To Many Conditions

Allergies and asthma can take a huge toll on health, not only due to their direct effects on the body but also because they are linked to other conditions – some of them life-threatening.

Studies have demonstrated an association between allergies, asthma, and suicidality. Researchers also have found that there is a greater incidence of suicidal thoughts during the allergy season.[7,8] The link between asthma and suicide is thought to be due to low serotonin levels caused by low oxygen (hypoxia).[9]

Seasonal allergies also are linked to sleep apnea, which in turn is linked to high blood pressure and cardiovascular conditions. Sleep apnea may be the reason why men who have seasonal or chronic rhinitis have on average a 3.5 mm Hg higher systolic blood pressure than those without allergic rhinitis.[10] Furthermore, scientists have discovered that asthma is a risk factor for obstructive sleep apnea.[11]

There's also a link between asthma, allergies, and migraines. People who have migraines are more likely to have asthma compared with people who don't suffer from migraines. In fact, researchers in the 1970s began referring to asthma as a "pulmonary migraine."[12]

Plus, a study published in *Cephalalgia* found that people who have both migraines and hay fever suffer from a more severe form of headache compared with people who have migraine but who don't have seasonal or year-round allergies.[13]

This supports the results of another study, which found that migraine patients who have allergic rhinitis and who received allergy shots experienced 52% fewer migraine attacks than those who didn't receive allergy shots.[14]

Other conditions and health challenges linked to asthma include an increased risk of pulmonary embolism and a more difficult time becoming pregnant.[15,16]

Additionally, an interesting study in the August 2013 issue of *Annals of*

Allergy, Asthma & Immunology found that boys who have a history of allergy or asthma also have an increased risk of attention deficit/hyperactivity disorder (ADHD). The increased risk of ADHD in boys with allergies and asthma may be due to medications used to treat these conditions.[17]

Controlling Total Burden

Mast cells and basophils – two types of white blood cells that trigger an inflammatory reaction – are primary culprits behind both allergies and asthma. An antigen (allergen) stimulates these two related cell types. Both mast cells and basophils are full of granules of histamine and other allergic chemical mediators. When allergen/antigens in the blood contact mast cells or basophils in sufficient numbers, a burst of histamine and other allergic mediators is released into the bloodstream. It is the histamine and other allergic mediators that trigger the misery of allergic reaction: runny, itchy nose and sneezing; watery, itchy red eyes; tickling and itching in ears, nose, and throat; skin rash; headache; asthma; and so on.

We each have a personal threshold as to how much exposure our bodies can handle before reacting to an allergen. This personal threshold often is determined by the total burden that a person is experiencing. Addressing the concept of total burden is one of the most critical aspects of treating allergies.

Total burden equals:

1. how much exposure the person is receiving to the actual allergen itself,
2. foods that can cross-react with the allergen,
3. factors that are comprising gut health,
4. factors that can make allergies and asthma worse,
5. hidden household sources, plus
6. factors that weaken immune health.

In order for a supplement regimen to have any effect against allergies or asthma, each of these six total burden factors must be addressed.

Minimize Exposure to Allergens

This is the most straightforward and direct step in treating allergies. There are some simple ways to help keep exposure to a minimum, including:

- Keep your home's doors and windows closed.
- Use the air conditioner rather than opening a window.
- Increase laundry water temperature, because research has shown that many people who have seasonal allergies also have dust mite allergies.[18]
- Wash bedding and pillows often.
- Limit outdoor activity, particularly in the morning (5 a.m. to 10 a.m.) and midevening.
- Keep track of pollen counts in your area and don't exercise outside during your allergen peak.
- Don't go outside more than necessary on windy days.
- Keep your car windows up and sun roof closed, and keep air on recirculate while driving.
- Shower prior to going to bed, including your hair, because pollen will collect on you throughout the day.
- Change your clothes after being outside; otherwise you will contaminate your inner sanctum.

Avoid Foods That Cross-React With Allergens

Certain foods cross-react with pollen allergens. If a person minimizes exposure to a grass or pollen allergen but continues to eat a related food, his or her hay fever symptoms may remain active.

Researchers now believe that most food allergies are acquired due to cross-reactivity with pollen allergens. Consequently, people who have pollen allergies might develop many plant food allergies – even to new foods that they've never eaten before.[19,20]

Studies have reported upon the following cross-reactivities[21–23]:

- an association between ragweed allergies and hypersensitivity to watermelon, melon, cucumber, and banana;
- birch pollen allergies and sensitization to hazelnut, apple, carrot, potato, kiwi, other vegetables, and soy. Up to 70% of birch-pollen allergic patients also develop an allergy to celery or carrot. Most of these patients suffer from allergy symptoms even outside of the birch pollen season, indicating that food caused allergy symptoms are to blame;
- mugwort pollen allergen and sensitization to celery, carrot, spices, nuts, mustard, and legumes;
- grass pollen allergies and sensitization to tomato, potato, pea, peanut, watermelon, melon, apple, orange, and kiwi.
- an association between plantain pollen allergy and melon hypersensitivity.

Furthermore, researchers also have established a connection between allergies to cypress pollen and peaches as well as between olive pollen and tomato, kiwi, potato, and peach.[20, 24]

Yet, the cross-reactivity isn't limited to only fruits and vegetables. One study found cross-reactivity between grass pollen allergies and allergies to egg white and pork.[25]

Clearly, it's critical that patients who suffer from hay fever also be tested for food allergies and intolerances.

Another food-related item to be wary of is alcohol – in particular wine and beer. First, wine and beer that contain high levels of sulfites can actually be lethal for some asthmatics.[26,27]

Second, wine and beer – especially red wine and dark beer – might make seasonal allergies worse because they contain histamines formed naturally as part of the wine- and beer-making process. People who are sensitive to histamine in alcohol are thought to have low levels of diamine oxidase, an intestinal enzyme that helps the body process histamine normally.[28]

Protecting the Gut

The gut is the daily filter to the burden that we unintentionally ➤

welcome into our bodies. A leaky gut (increased intestinal permeability) caused by overeating sugar and refined carbohydrates, antibiotic use, and emotional stress can allow food particles to pass through the walls of the colon and enter the systemic circulation. This can result in food allergies' developing or already-existing food allergies' worsening.[29]

Therefore, along with lifestyle measures such as eating a low-glycemic diet and reducing stress, taking a good probiotic is essential to strengthen the health of the intestines.[30] Furthermore, some studies have shown that probiotics can reduce the symptoms of seasonal allergies by enhancing immunity.[31]

Factors That Worsen Allergies And Asthma

Air pollution is another factor that adds to the total burden of a patient with allergies or asthma. In the modern world, people are exposed to both an increased amount of air pollution and a greater variety of pollutants.

The scientific literature is filled with studies demonstrating the damage that these pollutants cause in people with asthma.[32,33] Studies also show that pollutants from traffic exhaust contribute to the development of allergies.[34,35] In an animal study, diesel exhaust particle exposure increased rates of allergic reactivity and asthma and increased the production of antigen-specific IgE and histamine.[36]

Hidden Sources Inside the Home and Out

There are many sources of indoor pollution that can contribute to total burden of people suffering from allergies and/or asthma.

Indoor building materials, new furniture, and fresh paint may all contribute to allergies. In addition, perfluorocarbons used as stains as well as water repellents applied to furniture fabrics and carpeting can make allergies and asthma worse, as can phthalates (compounds added to plastics to make them more flexible). Dry cleaning, paint, paint thinner, glues, inks, nail polish and polish remover, and various building and construction materials are also hidden sources of allergies. All of these substances are linked to higher rates of allergic and respiratory problems.[36] They suppress Th1 function and lead the immune system into a Th2-dominant state, the type of immunity that is enhanced when a person is fighting an allergen.

Other substances strongly associated with asthma and allergies include herbicides and pesticides, which have been shown to induce Th2-dominant immune responses.[36]

Old mattresses, which can accumulate increased concentrations of dust mites and other allergens over time, are another household object that can contribute to total burden.

Surprisingly, feather pillows and bedding have been shown in numerous studies to have no effect on the risk of allergic rhinitis or asthma and to actually reduce the risk of wheezing. This is because down bedding accumulates dust mite allergens at a lower rate than synthetic bedding.[37–40]

Toxic mold inside the home is becoming another growing issue. Mycotoxins from *Stachybotrys chartarum*, otherwise known as toxic black mold, cause symptoms that can be confused with seasonal allergies including respiratory problems, skin inflammation, irritation of the mucous membranes, and fatigue. Toxic mold can cause severe health problems such as damage to internal organs and even death. It can even be a direct cause of asthma and allergic rhinitis, since proteins found in the mold are human allergens.[41–43]

It's critical to consider toxic mold as a cause of allergies or asthma, especially if the living environment was exposed to water or allergy symptoms occur year round.

Natural Support for Allergies and Asthma

One modality emerging as an effective treatment for allergies and asthma is acupuncture. A prospective, randomized, controlled clinical trial investigated the efficacy of acupuncture for treating asthma in children aged 6 months to 6 years.

The researchers randomly selected preschool children with medically diagnosed asthma and assigned them to an intervention or control group. Fifty-two children (26 intervention, 26 controls) were available for evaluation at 12 months. Although there were significant reductions in subjective asthma symptoms and in use of inhaled steroids in both groups at 3 months, the reduction in asthma symptoms and the reduction in use of inhaled steroids were significantly larger in the group being treated with acupuncture compared with the control group.[44]

Furthermore, in a randomized trial of patients with seasonal allergic rhinitis, acupuncture treatment resulted in an improved quality of life.[45]

Breaking The Inflammatory Cycle

Each factor that increases total burden in the body also increases inflammation. The inflammation that occurs in people who have asthma and allergic rhinitis creates a vicious cycle: the inflammation weakens the body, causing it to become less able to fight the inflammation, weakening the body even more.

The inflammation that results from chronic allergies triggers long-term changes in the structure of the affected organs and causes them to function abnormally.[3]

Participating in an anti-inflammatory lifestyle that includes 8 hours of restorative sleep and going to bed before 11 p.m. as well as minimizing sugar intake and participating in stress-reduction techniques and exercise is foundational to reducing inflammation.

Nettle leaf (*Urtica dioica*) also is an excellent choice for reducing inflammation in people suffering from allergic rhinitis. In vitro, a nettle extract inhibited several key inflammatory events responsible for seasonal allergy symptoms.[46] In one double-blind randomized study of 98 subjects with seasonal allergies, 58% of the subjects reported relief of most of their symptoms and 48% rated nettle leaf as being more effective than other over-the-counter medications.[47]

Protecting the Mucous Membranes

A dried yeast fermentate known as *Saccharomyces cerevisiae* (EpiCor) also has been shown to act as an anti-inflammatory while at the same time protecting the mucous membranes.[48]

The mucous membranes serve as the passageway through which allergens can gain entrance to the body. *Saccharomyces cerevisiae* can help protect the mucous membranes by increasing levels of salivary IgA, which creates a protective coating that keeps out allergens.[49,50] EpiCor also has reduced nasal congestion and rhinorrhea in subjects with allergic rhinitis during the 12-week period of the highest recorded concentrations of total pollen counts for a Midwest geographic area.[49]

Natural Antihistamines

Controlling histamine is another critical approach to battling the inflammation associated with seasonal allergies. *Petasites hybridus* (butterbur extract) has been shown in numerous randomized, controlled trials to act as an antihistamine and to reduce the symptoms of allergic rhinitis. ➤

Seasonal Allergies and Asthma

One review of the medical literature found that in six randomized, controlled studies of subjects with allergic rhinitis, butterbur extract was superior to placebo or equally effective as nonsedative antihistamines.[51] More independent studies are needed, since a manufacturer of butterbur extract provided financial support to three of the largest trials.

Another frequently effective approach is supplementation with vitamin C and quercetin.

In one study, children aged 6 to 12 years old who had increased vitamin C consumption had fewer allergic rhinitis symptoms, despite the lack of a difference in total serum IgE level or allergen sensitization.[53] Vitamin C also has acted as a powerful antihistamine.[52]

Quercetin not only inhibits histamine, which is responsible for the early phase of the allergic reaction, it also suppresses activation of eosinophils, the main type of cells called into action during the late phase of an allergic reaction.[54–56] Eosinophils play an important part in the development of persistent inflammation and tissue damage.[56] Quercetin also reduces clinical symptoms in animal models of asthma.[57]

Boosting Glutathione

Another important supplement to add to an antiallergy/antiasthma regimen is N-acetylcysteine (NAC).

Environmental chemicals can produce immune-system imbalances. Many of the environmental chemicals and pollutants associated with increased allergic tendency have been shown to enhance type 2 helper T cell (Th2) dominance, the T-helper cell pattern found in asthma, allergic rhinitis, and other type 1 hypersensitivity disorders.

Researchers have shown that glutathione depletion may be one possible reason for this T-helper cell imbalance. Preliminary evidence indicates that restoring glutathione levels with oral supplementation of NAC might be an effective option for reducing allergic rhinitis and asthma caused by environmental toxins.[58]

Additionally, in a rat model of allergic rhinitis, NAC – through its role as an antioxidant – suppressed the allergen-induced nasal inflammatory cascade.[59]

NAC also reduces the viscosity of mucus, so that the mucus is more easily expelled.[60]

Conclusion

The most effective way to heal the body of allergies and asthma is to reduce the total burden while at the same time supplementing with key nutraceuticals and engaging in lifestyle support measures. Addressing the total burden will make any supplement regimen or lifestyle approach more effective.

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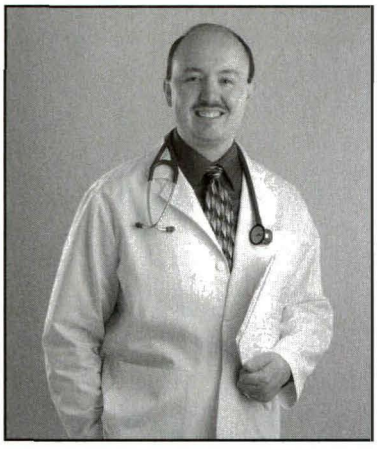

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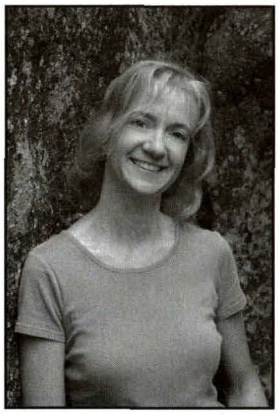

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Toward a Periodic Table of Allergens

by Kenneth Smith

The incidence of allergic disease is on the rise. According to the World Allergy Organization (WAO), environmental toxicity, socioeconomic factors, changes in weather, and a contaminated gene pool are all contributors.[1] Diagnosis can consist of costly and a sometimes painful series of tests to be followed by treatment that is often *not* effective. Allergy research, though, is becoming more refined due to increasing knowledge of immunology and molecular cross-reactivity, and the advent of component-resolved diagnosis. Combined, these areas offer consideration that there may be only a few allergens that could address hundreds of allergies. Future research may reveal a periodic table of allergens.

An allergy is an inappropriate immune response to an antigen; more specifically, a reaction to an allergen or allergy-provoking substance. Symptoms may occur when exposure to an allergen sensitizes a person to that allergen. Responses may vary considerably and be manifested as food allergies, respiratory-related ailments such rhinitis and asthma, skin disorders such as eczema, and reactions to insect bites and stings. Exposure to pollen, for example, may cause watery and itchy eyes, runny nose, and difficulty in breathing. Ingesting or inhaling peanut, in turn, may send a person into life-threatening anaphylactic shock. Diesel exhaust particles are known to upregulate cytokine and chemokine production and exacerbate, if not cause, respiratory allergies.[2] Other environmental factors include pollution, tobacco smoke, and ozone.[3]

Joseph B. Miller, MD, a leading allergy researcher, found that food hypersensitivity contributed to a spectrum of problems ranging from the more traditional skin and respiratory disorders to arthritis, migraines, and even learning disorders, saying that "cerebral responses to allergenic foods usually take the form of stimulation, depression, or inappropriate behavior." Miller cited food additives as yet another reason for the increase in allergy. He also held that allergy may be misdiagnosed as an idiopathic or psychosomatic disorder.[4] Other researchers have linked back pain and spasm as well as depression to allergy.[5]

In his book *Relief at Last!*, Miller wrote the "body has a marvelously complex and comprehensive network of immunologic and biochemical tools for maintaining stability to defend itself from many conditions and substances such as allergens."[6] Therefore, as with other disease allergic responses represent instances where an external agent has thrown the internal mechanisms that maintain health out of balance; that is, an allergen disrupts homeodynamics.

Increasing Allergy

In the US from 2001 to 2009, the Centers for Disease Control (CDC) reported that the incidence of asthma increased from 7% of the total US population to 8% and that hay fever and sinusitis together affected about 20% of adults.[7] Food allergy affects about 4% of adults and 6% to 8% of children under 4 years of age.[8] It is estimated that all forms of allergy combine to be the fifth leading chronic disease.[9]

While the rise in allergic disorders is a problem confronting the general population, perhaps because of all of the causative factors it appears that young people are taking the brunt. From 1997 to 2007, the CDC indicated that the food allergy rate among children under 18 rose 18%, and from 1997 to 2011 skin allergy increased about 5%. The incidence of hospitalization of children under 18 attributable to food allergy increased from roughly 2600 per year in the late 1990s to an average of over 9500 per year in the mid-2000s. Twenty-nine percent of children under 18 with food allergy also had asthma, compared with only 12% of children who did not have food hypersensitivity. Children having coexisting conditions of food allergy and asthma were more likely to experience anaphylactic reactions and be at higher risk of allergen-induced fatality.[10]

According to the WAO, 30% to 40% of the global population now has one or more allergic conditions. Allergic rhinitis, inflammation of mucous membrane inside the nose, affects an estimated 400 million people – including 10% to 30% of all adults and 40% of children – with 300 million people suffering from asthma. Occupational asthma accounts for 15% of asthma among adults.[11]

Some researchers attribute the higher incidence of allergy to expanding affluence. Citing that

hypersensitivity affects up to 50% of children in developed countries, they point to a loss of innate protection against allergens that once was derived from farm life and exposure to animals, few or no vaccinations, and drinking unpasteurized milk.[12] The thinking is that traditional farm life exposed people to many allergens and infectious agents that caused subclinical infections. These stimulated the immune system in variety of ways so that it could later handle allergen overloads. In short, some investigators maintain that allergy is the price paid by the children of the wealthy middle classes for their current relative freedom from those diseases which have afflicted humanity through society's evolution.[13]

While this view falls under the umbrella of the hygiene hypothesis of allergy, the hygiene hypothesis extends beyond considerations of farm life. As the term indicates, it speaks to general cleanliness. In a study conducted in Turkey, for instance, researchers found that the prevalence of asthma and atopic disease was significantly higher in developed areas such as those that contained central city schools as compared with lesser developed areas where they found slum schools. Allergic diseases were also determined to be more common in children living in apartments, especially if there were more rooms and the occupants enjoyed economic well-being.[14]

In another study, investigators held that while the hygiene hypothesis is not completely accepted, it does offer a foundation to more fully explore allergy. They point to rapid changes in society including those of diet, antibiotic use, and the environment – all of which have altered the microbiota in the gut and therefore some immune responses.[15]

Because of all of these influences, allergy incidence is expected to continue increasing, and the need for new approaches to treating hypersensitivity is unmistakable. WAO and other organizations call for increased diagnostic capability and new therapies.[16] The understanding and therapeutic exploitation of cross-reactivity offer a positive response to this call.

Cross-Reactivity

In terms of allergy, cross-reactivity occurs when an immune response to one allergen results in reactivity to structurally related components of other allergens.[17] The effect is that sensitivity to one allergen may produce symptoms when exposed to apparently unrelated substances. So a person allergic to lima bean might also be allergic to mesquite, as these contain a similar molecular makeup.[18]

Decades of lab and clinical research by investigators associated with the Institute for Therapeutic Discovery, founded by John McMichael, a PhD immunologist/virologist, indicates that via cross-reactivity there may be only a handful of allergens that can address a range of allergies, meaning there could be a periodic-like table of allergens. Just as a relatively few elements comprise everything in our known world, a few allergens may combine in many ways to induce an assortment of allergies.

Throughout his career, McMichael has translated various ideas into different therapeutic approaches. In addition to founding the institute, for instance, McMichael is the founder and CEO of Beech Tree Labs Inc., a for-profit biopharmaceutical company focused on a novel cellular communication platform designated Resonant Molecular Signaling (RMS). Most of the agents in this therapeutic platform are naturally occurring molecules employed at physiological concentrations to address a range of chronic disorders such as urinary incontinence, herpes, and wound healing. Giving evidence of efficacy, various RMS agents have undergone 16 successful FDA-authorized clinical trials, with the results of each trial indicating that these formulations produce only placebo-level adverse events.

RMS continues to develop from McMichael and his professional network's efforts to synthesize different ideas with the goal of reducing those ideas to practice. McMichael applies this same diligence when addressing hypersensitivity. For over 20 years, his lead allergy researcher has been Sue Killian, an institute scientist who is an allergy sufferer herself.

McMichael emphasizes it is the individual's response to a molecule that determines if it is an allergen; otherwise there would be a universal response. Fortunately, only a few of the huge number of molecules affecting us through the day have become allergens. More specifically, the hypersensitive patient's reaction is to an epitope, the part of an antigen that the immune system responds to and which may be a linear amino acid sequence or a folded structure of a particular allergenic molecule. The basis of allergy-related cross-reactivity is that the same epitope can be found in many types of pollen, foods, and other allergy-inducing substances.

Knowing about cross-reactivity has immeasurable practical value for allergy sufferers. Birch pollen, for example, contains several highly cross-reactive allergens.[19] One of these allergens is found in apples, cherries, pears, celery, carrots, and parsley. Another is found in apples, celery, carrots, potatoes, tomatoes, pumpkin seeds, and chamomile. Having a fruit salad and a cup of chamomile tea during birch pollen season might therefore produce or exacerbate allergy symptoms. Even beyond pollen and food, in the same manner roach-sensitive patients may also be sensitive to shrimp, and exposure to cross-reactive roach allergens may produce a reaction to the same allergens found in shellfish. Ragweed is also on the list as highly cross-reactive. By knowing these connections, people can modify their lifestyle to help minimize symptoms.

Using standard immunological tests, Killian is identifying cross-reactive peptides and proteins between pollens and foods with the aim of eventually determining the most cross-reactive among them. When a particular pollen or food

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has a great number of cross-reactive allergens, McMichael refers to them as a "mother allergen." "Getting to these common denominators is the point of Killian's research," he says.

Due to its highly cross-reactive nature, mesquite has been one focus of Killian's work. She has published results indicating that mesquite tree pollen has more allergens than previously recognized.[20] Thus far, she has identified 19 trees and 26 foods – including orange, onion, tomato, coconut, and wheat – that cross-react with mesquite. Further research will define which of these are the most cross-reactive and relevant to human allergy. Furthermore, researchers in India have found that mesquite has three additional allergens and have documented its cross-reactivity with other tree pollens and lima beans. These investigators also maintain that mesquite can be employed to enhance diagnosis and reduce the number of allergens needed for treatment without reducing efficacy.[21]

Treatment

A patient can now go to an allergist and be tested for 200 different substances and then treated for a number of allergies as though they are unrelated. However, since sensitivity to one allergen may simultaneously sensitize the person to other seemingly unrelated allergens, a patient may experience a broadening scope of allergic reactions simply because those foods or pollens share common antigenic denominators. Since coconut cross-reacts with mesquite pollen, for example, a person allergic to mesquite might increase the intensity of the mesquite-induced reaction if he or she were to eat coconut during mesquite pollen season.

Treatment utilizing cross-reactivity consists of reversing this principle. That is, a new form of therapy might consist of nonspecific desensitization whereby one highly cross-reactive antigen such as found in mesquite is employed to neutralize the responses induced by many other antigens. For example, when a person who is allergic to coconut and mesquite is treated only for the mesquite allergy, the negative responses to coconut also disappear. Accordingly, a better understanding of cross-reactivity holds potential in that treatment with just one cross-reactive allergen can simultaneously reduce the allergic responses from many different foods and pollens that harbor that same allergen. As a result, treatment becomes greatly simplified, more effective, and less costly in terms of time, money, and suffering.

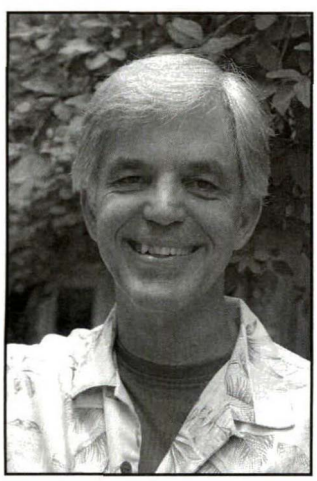
There are physicians who are currently using this approach in treating allergies. For instance, Susan Tanner, MD, an environmental medicine practitioner near Atlanta, has used mesquite to address nasal allergies, many food allergies, and migraine headaches. For another example, Allan Lieberman, MD, who established the Center for Occupational & Environmental Medicine in Charleston, South Carolina, and is nationally recognized for his expertise in allergy, uses mesquite to effectively reduce the number of allergy tests. He says that it is particularly useful for small children and those who cannot afford testing. He also finds positive results when using mesquite to treat autistic children for allergies.

A Periodic Table of Allergens

Component-resolved diagnosis (CRD) is a relatively new method of precisely determining allergy related to a specific portion of the whole pollen or food allergen. A benefit of CRD is that it can reveal the cross-reactive molecules in seemingly unrelated pollens and foods. Molecules known to have high cross-reactivity can then be used to simplify treatment for patients having sensitivity to a variety of substances. In addition, researchers maintain that finding the exact molecules within an allergenic food that actually cause the reaction is a step toward minimizing anaphylaxis.[22]

Mesquite is highly cross-reactive because it is polyvalent; that is, it is a complex collection of allergenic molecules. It therefore possesses a spectrum of potential cross-reactivity beyond that of any one of the allergens it contains. Future research may reveal that monovalent antigens, such as human and bovine serum albumin, exhibit cross-reactivity. For now, however, the focus of institute research is on polyvalent substances as they deliver a clearer picture of cross-reactivity and so more quickly illuminate the prospect of enhanced treatment.

Building on CRD and cross-reactivity illustrates McMichael's refinement of thought in seeking new allergy treatment. From a general



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approach wherein there are thought to be innumerable allergens producing any number of allergies, to a cross-reactivity method of treating several allergies with one molecule to CRD where specific epitopes are revealed, the funnel of research has steadily narrowed toward the idea that like the periodic table of elements, there could be a similar table of allergens.

Combining and recombining elements on the periodic table form every structure we know. Some 118 elements comprise our known physical universe simply by different arrangements of those elements. Chairs, windows, and trees are different but are all composed of common denominator elements. The reactive epitopes of mesquite could likewise represent individual components of a "periodic table of allergens," as these same epitopes can be found in banana, peanut, ragweed, chicken, and many other allergens. They're just part of different combinations of molecules, and these shared epitopes are at the heart of cross-reactivity.

Therefore, while these allergen are thought to be different, if they share a common feature – the same epitope – both laboratory studies and clinical practice demonstrate that this common denominator can be neutralized no matter the number of different allergens containing it. Just as the example of mesquite has been shown to neutralize an assortment of diseases, there might be a handful of mother allergens that could address most, if not all, allergies.

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What is Actionable Intelligence?

by Jacob Schor, ND, FABNO

It is often difficult to know when there is adequate information to put some action into motion. I suppose that it depends on the risk involved, the risk of doing nothing versus the risk of doing something.

I'm thinking about this because of the paper published in the *New England Journal of Medicine* by Bao et al. on November 21, 2013. In it Bao's team elegantly suggests that nut consumption has an inverse association with mortality; that is, the more nuts people eat, the longer they live.[1]

Bao and colleagues analyzed data from two large, long-term, prospective cohort studies separately and then in combination checking for an association between nut consumption and mortality, both total mortality and cause-specific mortality.

They used large cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPS). The NHS is a prospective cohort of 121,700 female nurses enrolled in 1976. The HPFS is a prospective cohort of 51,529 male health professionals enrolled in 1986. The current study eliminated participants without complete data or who had a history of cancer, heart disease, or stroke, so in the final analyses data from only 76,464 women and 42,498 men were included. Still, if you multiply those people by 30 years, the researchers still had 3,038,853 person-years of data to analyze. During that time 16,200 women and 11,229 men died

Nut eating patterns were tracked using food-frequency questionnaires administered every 2 to 4 years. The primary study end point was death from any cause. The researchers also sought associations with specific causes of death.

The bottom line was that the more nuts these people ate, the less likely they were to die: nut consumption was inversely associated with total mortality among both women and men. The more nuts they ate, the lower their risk of dying during the study. Eating nuts daily was associated with a 20% lower risk of dying compared with those who didn't eat nuts at all.

Eating nuts even less than once per week lowered risk of dying 7% compared with never eating nuts. Eating nuts once per week cut risk by 11%, 2 to 4 times per week cut risk by 13%, 5 to 6 times cut risk by 15%, and daily nut eating was associated with a 20% lower risk. This inverse association was also statistically significant for deaths from cancer, heart, and respiratory disease.

This study is likely the strongest epidemiological evidence ever published suggesting that we should eat more nuts. The size and length of the study added power to the statistics, the 3 million patient-years of data is huge. This wasn't a hasty or sloppy study. In analyzing the data, these Harvard epidemiologists made every effort they could to counter possible confounders that could have been responsible.

Still, when it came time for the conclusion, they wrote, "... epidemiologic observations establish associations, not causality, and not all findings from observational studies have been confirmed in controlled, randomized clinical trials."

True enough, I suppose; but if this isn't enough, what is?

This is like that elephant and blind men story. Epidemiologists and public health researchers see the world differently than we do, with greater caution Where we might jump to translate this information into clinical practice, these researchers hold back, afraid to commit.

They have reason to be reticent. Randomized controlled trials (RCTs) have had mediocre success in confirming epidemiologic predictions. Recall the 2013 paper by Moorthy et al. that compared the findings of RCTs with the epidemiological data that the trials were meant to confirm. In only 23 out of 34 associations did the results from meta-analyses of epidemiological studies and of RCTs point in the same direction, and in only 6 of those 23 associations were the findings statistically significant. In the remaining 11 out of 34 associations, meta-analyses of epidemiological studies and of RCTs pointed in opposite directions. Of the 12 out of 34 associations in which the association between RCT and epidemiology was statistically significant, only 6 of the results were in the direction predicted by epidemiological studies; the results of the other 6 were in the opposite direction.[2] Basically it seems that it's kind of a coin-flip whether past epidemiological associations will be confirmed in RCTs. We should probably give Bao et al. a bit of slack if they sound hesitant.

Moorthy's results should be taken with a grain of salt. They considered studies conceived back in the age when nutritional interventions were simple, when nutrient unideficiencies were the cause of diseases. Unfortunately, not every disease has proved to be as straightforward to treat as scurvy or pellagra.

If modern nutritional researchers seem shy, remember that they have survived the ignominy of the CARET failure. That was the study in which beta-carotene increased rather than lowered risk of lung cancer in smokers.[3–5] They were also left with pie on their faces when SELECT found that vitamin E and selenium supplements were associated with a higher risk of getting prostate cancer.[6,7] Same with the more recent SELECT paper which reported that increased omega-3 fats in the blood were associated with an increased risk for prostate cancer.[8] It's easy for us on the outside to think that we know why their studies failed. It's got to be a huge disappointment and embarrassment for the people involved.

These past failures, though, are from studies that looked at single nutrients. Nuts may be a different story, as they are not a single nutrient but complex biological substances. It makes more sense to test "food supplementation or broad dietary change" in populations.[9] It's more likely that these food study results will hold.

Certainly we should consider the results of this current Bao nut study in the context of other earlier studies about nuts. There is a impressive amount of positive work already published on nuts. Observational and clinical trials suggest that nut consumption has beneficial effects on coronary heart disease and its intermediate biomarkers.[10–12] As early as 2003, the Food and Drug Administration concluded that 1.5 oz. of nuts per day "may reduce the risk of heart disease."[13]

Granted that epidemiology alone may sometimes steer us off course, but we already have RCTs that suggest multiple benefits from eating nuts. The PREDIMED Trial, the Spanish study that gave people at high risk for cardiovascular disease supplemental nuts or extra-virgin olive oil to eat, reported significant reductions in cardiovascular events in those consuming about an ounce of nuts per day. [14] In fact, the PREDIMED trial results may actually trump this current paper, as PREDIMED was a randomized prospective primary prevention trial and the Bao study is only observational. Still the sheer size of the Bao's cohorts makes it hard to ignore.

Bao's numbers are not that different from the numbers that the Adventist Health Study reported about nuts two decades ago. In those early

findings, eating nuts 5 or more times per week compared with less than once per week was associated with reduced total mortality with hazard ratios ranging from 0.56 to 0.82.[15–17] That is pretty much the same ballpark. Since those early Adventist studies, there have been studies associating nut-eating with reductions in predictors of chronic disease including oxidative stress, inflammation, visceral adiposity, hyperglycemia, insulin resistance, and endothelial dysfunction.[18–23]

Other prospective cohort studies have associated increased nut intake with reduced risks of type 2 diabetes, metabolic syndrome, colon cancer, hypertension, gallstone disease, diverticulitis, and even death from inflammatory diseases.[24–30]

This current study is a change in that it does not concern itself with anything other than the bottom line: whether nuts change the risk of dying. One would think that when all this is added together, it would be adequate. What end of the elephant do we have a hold on?

In clinical practice, our mission is improving patient outcomes. Our bottom line is disease reduction. We compare risk versus benefit constantly. The potential payoff from eating more nuts looks good. The risk side of the equation looks empty. If by some fluke confounders exist and it turns out that nuts are a dud, that they don't really reduce death and morbidity, it's still likely that our patients will be no worse off; eating nuts will not hurt them.

This is where our perceptions as clinicians differ from the view of researchers. They can debate as long as they want, especially if they have tenure. We need to give our patients sound advice today that will improve their health tomorrow. Association may not be causality, but nevertheless, all things considered, particularly the low risk versus potential benefit, it now seems absurd not to tell most of our patients to eat a daily portion of nuts.

Notes

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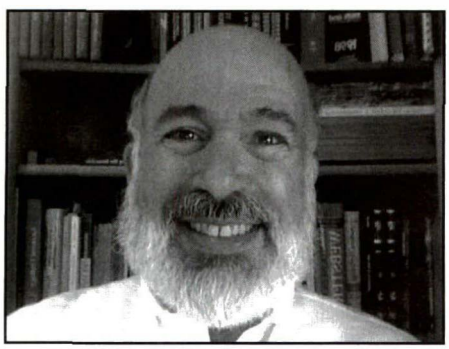

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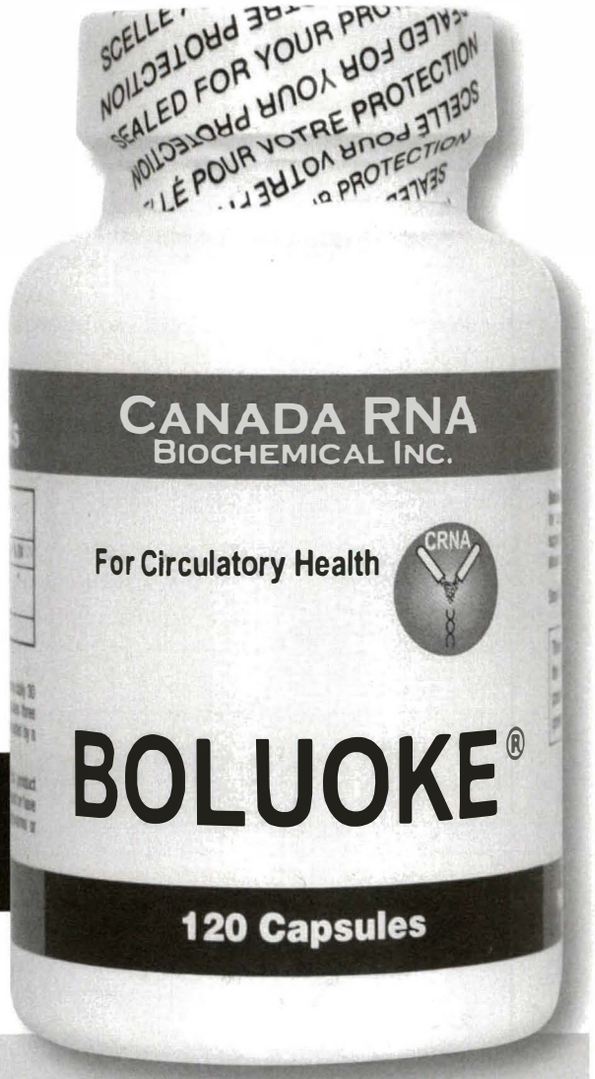

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A Proactive Approach to Memory Loss

review by Neil Raff, MD

What You Must Know About Memory Loss & How You Can Stop It
by Pamela Wartian Smith, MD, MPH
Square One Publishers, 115 Herricks Rd., Garden City Park, New York 11040
 softcover; $15.95; 196 pp.

Memory loss is a growing problem in an increasingly aging American population. Dr. Pamela Smith's new book *What You Must Know About Memory Loss* serves as an excellent guide to this common issue. Using plain language and with a firm grasp of the material at hand, Smith eliminates the fear and mystery so often attached to this complex problem and makes it comprehensible to the average reader.

The book is divided into two parts. In the first part, Smith outlines the various types of cognitive decline and details the factors that may contribute to them: hormonal imbalances, heavy metal poisoning, cardiovascular disease, inflammation, and insomnia. This part is interactive: through questionnaires, readers are encouraged to identify whether any of these factors might be affecting them. In the second part, Smith encourages her readers to take a proactive approach to memory loss. By improving sleep, diet, stress, and physical activity levels, Smith believes that we can forestall and possibly even prevent many of the more aggressive forms of cognitive decline.

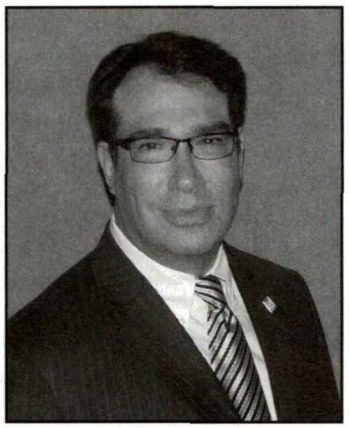
While acknowledging that much still remains unknown about Alzheimer's disease and other forms of dementia, this book is a useful primer for those wishing to gain a basic understanding of memory loss. It is clearly written and highly accessible, making it ideal for the average reader. That said, physicians and other health-care professionals may also be interested in this book, owing to its masterly command of current medical literature on the topic; hundreds of studies are either discussed explicitly or referenced in a convenient "Resources" section in the back. Doctors may want to recommend this book to their patients, so that together they may develop a unified approach toward better mental acuity and overall wellness. ◆

Best of Naturopathic Medicine 2015

The *Townsend Letter* is pleased to announce our seventh Best of Naturopathic Medicine competition. Naturopathic students, faculty, researchers, and practitioners are invited to submit research papers, reviews, and articles. Selected papers will be published in our February/March 2015 issue. The author of the winning paper will be awarded $850. Runner-up papers will be published and authors will receive an honorarium.

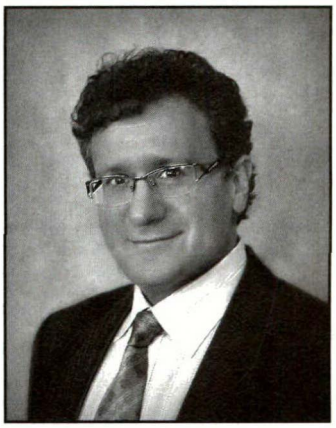
Papers submitted should be 1500 to 3500 words and referenced. Author guidelines are available at the *Townsend Letter* website: www.townsendletter.com. Papers should be submitted digitally, preferably as a Microsoft Word document. Papers authored by multiple writers are acceptable; the lead author should be an ND graduate or candidate of an accredited four-year naturopathic school. Papers submitted for the competition may not be submitted to other publications or have previously been published. All entries must be submitted by October 31, 2014.

Send papers to editorial@townsendletter.com. The subject line should read: "Paper for Best of Naturopathic Medicine 2015."



Anti-Aging Medicine

by Ronald Klatz, MD, DO, and
Robert Goldman, MD, PhD, DO, FAASP
www.worldhealth.net



The Role of Diet in Heart Disease: An Anti-Aging Perspective

The US Centers for Disease Control and Prevention (CDC) reports that heart disease continues to rank as the leading cause of death in the US. Approximately 600,000 Americans die of heart disease every year – equating to roughly 1 in every 4 deaths.

Nearly half of all Americans (49%) have at least one of the three primary risk factors for heart disease; namely, high blood pressure, high LDL cholesterol, or smoking. Importantly, a number of other medical considerations may also put people at a higher risk for heart disease, with excess weight positioned as a leading factor. Borge G. Nordestgaard and colleagues from Copenhagen University Hospital (Denmark) studied data collected on 71,527 men and women enrolled in the Copenhagen General Population Study, for whom BMI, waist measurement, and blood pressure and lab tests to identify metabolic syndrome were conducted. The team found that among subjects who did not have metabolic syndrome, the hazard ratio for heart attack compared with normal-weight participants was 1.26 in overweight individuals and 1.88 in those who were obese. They write: "These findings suggest that overweight and obesity are risk factors for [myocardial infarction] and [ischemic heart disease] regardless of the presence or absence of metabolic syndrome and that metabolic syndrome is no more valuable than BMI in identifying individuals at risk."

To protect heart health, the CDC recommends that people consume a healthful diet that is low in salt, total fat, saturated fat, and cholesterol and rich in fresh fruits and vegetables. In that it is generally agreed that dietary choices can affect heart health, in this column we share the latest research that underscores the role of diet in heart disease.

Heart disease [Web page]. US Centers for Disease Control and Prevention, http://www.cdc.gov/heartdisease/index.htm. Accessed 27 Jan. 2014.

Heart disease facts [Web page]. US Centers for Disease Control and Prevention, http://www.cdc.gov/heartdisease/facts.htm. Accessed 27 Jan. 2014.

Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. *JAMA Intern Med.* November 11, 2013.

Increase Fiber to Decrease Heart Disease Risk

As little as 1 extra portion of whole grains plus more fruit and vegetables may lower a person's risk of heart disease. Victoria J Burley and colleagues from the University of Leeds (UK) completed a study of data contained in six electronic databases from the US, Europe, Japan, and Australia, compiled on healthy subjects and concerning dietary fiber intake. The data revealed that the likelihood of a cardiovascular disease or coronary heart disease event steadily lowers with increasing intake of total, insoluble, fruit and vegetable fiber. For soluble fiber, a higher reduction was seen in cardiovascular disease risk than coronary heart disease risk; for cereal fiber, the reduced risk of coronary heart disease was stronger than the association with cardiovascular disease. Notably, a significantly lower risk of both cardiovascular disease and coronary heart disease was observed with every additional 7g per day of fiber consumed. Writing, "Greater dietary [fiber] intake is associated with a lower risk of both cardiovascular disease and coronary heart disease," the study authors submit: "Findings are aligned with general recommendations to increase [fiber] intake."

Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ.* 2013 Dec 19;347:f6879.

Apple a Day May Keep Heart Problems Away

Recommending an apple a day to all adults aged 50 years and over may prevent or delay approximately 8500 deaths due to heart attacks and strokes every year, in the UK alone. Further, the protective effect of a daily apple may be equivalent to giving statins to everyone over 50 years who is not already taking them. Adam Briggs and colleagues from the University of Oxford (UK) utilized a mathematical model to analyze the effect of prescribing either a statin for those not already taking one, or an apple a day to everyone aged 50 years and over, on the most common causes of vascular mortality. The resulting data that suggested that offering a daily statin to 17.6 million

more adults would reduce the annual number of vascular deaths by 9400, but offering a daily apple to 70% of the total UK population aged over 50 years (22 million people) would avert 8500 vascular deaths. Further, the diet-based intervention of an apple a day diverted the side effects of statins prescriptions, which can include muscle disease (myopathy) and diabetes. Writing, "Both nutritional and pharmaceutical approaches to the prevention of vascular disease may have the potential to reduce UK mortality significantly," the study authors conclude: "A 150 year old health promotion message is able to match modern medicine and is likely to have fewer side effects."

Briggs ADM, Mizdrak A, Scarborough P. A statin a day keeps the doctor away: comparative proverb assessment modelling study. *BMJ*. 2013;347:f726.

More Magnesium May Lower Death Risk

Consuming a diet abundant in magnesium-rich foods may reduce mortality among people at high cardiovascular risk. Spanish researchers completed a prospective study of subjects enrolled in the Prevention con Dieta Mediterranea (PREDIMED) study, in which participants at a high risk of cardiovascular risk were randomly assigned to consume a Mediterranean diet supplemented with nuts or olive oil, or a low-fat control diet. Following the subjects for 5 years, the team found that those with the highest average intakes of magnesium (442 mg/day) were at 59% reduced risk of cardiovascular mortality, a 37% reduction in cancer mortality, and a 34% reduction in all-cause mortality, as compared with those with the lowest average intakes of magnesium (312 mg/day). The study authors conclude: "Dietary magnesium intake was inversely associated with mortality risk in Mediterranean individuals at high risk of [cardiovascular disease]."

Guasch-Ferre M, Bullo M, Estruch R, et al.; on behalf of the PREDIMED Study Group. Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular risk. *J Nutr*. 2013 Nov 20.

Coffee Compounds Assist Heart Health

The cells that line blood vessels, known as the endothelium, perform many functions, including to maintain elasticity of blood vessels and regulate the activity of immune cells. Endothelial function is measured by detecting transient increases in blood flow, a marker known as the reactive hyperemia index (RHI). Japanese researchers enrolled a group of healthy, nondiabetic men in a study in which each was randomly assigned to consume a 75 g glucose load either with or without green coffee bean polyphenols. The team observed that blood glucose and insulin levels increased after both interventions, and there were no differences between the groups. However, the reactive hyperemia index rose significantly in the polyphenol group, as compared with their starting levels. The study authors conclude: "These findings suggest that a single ingestion of [coffee polyphenols] improves peripheral endothelial function after glucose loading in healthy subjects."

Ochiai R, Sugiura Y, Shioya Y, Otsuka K, Katsuragi Y, Hashiguchi T. Coffee polyphenols improve peripheral endothelial function after glucose loading in healthy male adults. *Nutr Res*. 18 November 2013.

Eating Walnuts Reduces Cardiovascular Risk

Eating whole walnuts or walnut oil can reduce the risk of cardiovascular disease by improving blood vessel function and helping to remove excess cholesterol from the body. Penny Kris-Etherton, Distinguished Professor of Nutrition at Penn State, and colleagues gave 15 participants with elevated blood cholesterol 1 of 4 treatments: 85 g of whole walnuts, 6 g of skin, 34 g of defatted nutmeat, or 51 g of walnut oil. The researchers evaluated biochemical and physiological responses in the participants before the treatments were administered and again 30 minutes, 1 hour, 2 hours, 4 hours, and 6 hours after administering the treatments. The process was then repeated for each of the remaining 3 treatments. Results showed that consumption of walnut oil helped to reduce cardiovascular risk by preserving the function of endothelial cells, the cells that line blood vessels. The researchers also found that walnut oil enhanced the ability of HDL cholesterol to remove excess cholesterol from the body. "Our study showed that the oil found in walnuts can maintain blood vessel function after a meal, which is very important

given that blood vessel integrity is often compromised in individuals with cardiovascular disease," said Claire Berryman, graduate student in nutritional sciences, at Penn State. "Implications of this finding could mean improved dietary strategies to fight heart disease." Walnuts and walnut oil are a rich source of alpha-linolenic acid, gamma-tocopherol, and phytosterols.

Berryman CE, Grieger JA, West SG, et al. Acute consumption of walnuts and walnut components differentially affect postprandial lipemia, endothelial function, oxidative stress, and cholesterol efflux in humans with mild hypercholesterolemia. *J Nutr*. 2013 Apr 24.

Sugar Excess May Damage Heart

Too much sugar can set people down a pathway to heart failure, according to a study from researchers at the University of Texas Health Science Center at Houston (US). Heinrich Taegtmeyer and colleagues report that a single small molecule, the glucose metabolite glucose 6-phosphate (G6P), causes stress to the heart that changes the muscle proteins and induces poor pump function, leading to heart failure, as demonstrated by an animal model as well as in tissue taken from patients at the Texas Heart Institute. In that G6P can accumulate from eating too much starch and/or sugar, the study authors "implicate a critical role for G6P in load-induced mTOR activation and [endoplasmic reticulum] stress," proposing "Glucose metabolic changes precede and regulate functional (and possibly also structural) remodeling of the heart."

Sen S, Kundu BK, Wu HC, et al. Glucose regulation of load-induced mTOR signaling and ER stress in mammalian heart. *J Am Heart Assoc*. 2013 May 17;2(3):e004796.

Heart Disease Linked to Dementia Risk

Be mindful that heart disease can trigger adverse changes in the health of other parts of the body. For example, women with cardiovascular disease, particularly those who have suffered a heart attack, tend to be at increased risk for dementia. Findings from the Women's Health Initiative (WHI) Memory Study, an ancillary to the Women's Health Initiative study, suggest that cardiovascular disease may be linked to an increased risk of cognitive decline. Bernhard Haring and colleagues from the University of Wurzburg (Germany) studied data collected on 6455 postmenopausal women enrolled in the WHI memory study, including 895 women with cardiovascular disease at the study's start. After an average of 8.4 years of follow-up, the data revealed that those women who had suffered a heart attack were at twice the risk for cognitive decline, as compared with women with no heart attack history. Additionally, those women with cardiovascular disease were 29% more likely to experience cognitive declines, as compared with women without cardiovascular disease. The study authors urge that "more research is warranted on the potential of [cardiovascular disease] prevention for preserving cognitive functioning."

Haring B, Leng X, Robinson J, Johnson KC, Jackson RD, Beyth R, et al. cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study. *J Am Heart Assoc*. 2013 Dec 18;2(6):e000369.

To stay updated on the latest breakthroughs in natural approaches to promote cardiovascular health, visit the World Health Network (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, your weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity. ◆

Monthly Miracles

by Michael Gerber, MD, HMD
contact@gerbermedical.com

Kidney Stone Relief

It's great to have a few miracles in your armamentarium, and none is more appreciated than the rapid relief of kidney stone pain. Sonnets have been written about the severity of renal lithiasis colic. The spasmodic nature of the pain, nausea, vomiting, pain radiating from the flank into the groin with fever, blood and/or white cells in the urine are usually a pretty straightforward diagnosis confirmed by an intravenous pyelogram (IVP). The pathophysiology of kidney stones is well summarized in Wikipedia. Current urological approaches to treatment are also summarized there. It is good to remember that stones measuring 5 mm or less usually pass by themselves, and with stones of 5 to 10 mm the rate of spontaneous passage is only about 53% and may require more intervention. Stones high in the ureter pass only 48% of the time compared with 79% of stones near the bladder.

Kidney-Bladder Distinct Meridian Therapy Amplified with Neural Therapy and Homeopathics: 10 Minutes Until Relief of Pain

To begin, I offer thanks for the kind permission of Joseph Helms, MD, to use material from his great textbook *Acupuncture Energetics: A Clinical Approach for Physicians*.[1] I always remember his video lecture from the UCLA Medical Acupuncture Training Course in 1997 on the Kidney-Bladder distinct meridian. It showed Helms jingling a metal urinal with kidney stones in it and roses sticking out the top from a grateful patient who passed his kidney stones after acupuncture treatment. Likewise, thanks to Dietrich Klinghardt, MD, PhD, teacher of neural therapy (NT) from Germany and medical innovator who brought us the power of procaine for normalization of the autonomic nervous system, especially for pain relief. One can't forget the Heel Company from Baden-Baden, Germany, which provides powerful combinations of homeopathic remedies, and Harry Philibert, MD, from New Orleans who brought us the IRR (infraspinatus respiratory reflex) on the scapulae, for immediate relief of asthma and pulmonary conditions and supraspinus injections of the dorsal spine for pain relief everywhere. Dr. Philibert passed away in 2008 at age 81.

Combining NT injections in intradermal wheals of procaine with Spascupreel over acupuncture points relating to the kidneys makes a happy combination of therapies for quick results in kidney stone colic. Draw up 3 cc of procaine (1% solution buffered to a pH of 7 with potassium hydroxide and no epinephrine) with 1 ampoule of Spascupreel containing *Aconitum napellus* 6x, *Agaricus muscarius* 4x, *Ammonium bromatum* 4x, *Atropinum sulphuricum* 6x, *Chamomilla* 3x, *Colocynthis* 4x, *Cuprum sulphuricum* 6x, *Gelsemium sempervirens* 6x, ➤

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Magnesia phosphorica 6x, *Passiflora incarnata* 2x, and *Veratrum album*. Use a 30 gauge needle (or 27 or 25 gauge), inject intradermal wheals over the Kidney-Bladder distinct meridian points of Bladder 10, Bladder 40, and Kidney 10 with the addition of the Kidney Shu point, Bladder 23, all bilaterally. Bl 10 is two fingerbreadths on each side of the occipital notch. Bl 40 is in the middle of the knee crease and Kl 10 is in the medial aspect of the knee crease. BL 23 is three fingerbreadths lateral to each side of the back midline at about the level of the iliac crest. Relief of pain and nausea is almost immediate. Of course, using acupuncture needles in dispersion, twiddling counterclockwise, is also effective, as is adding electrical stimulation of 40 to 80 hertz, alternating positive and negative electrodes to the acupuncture needles. Procaine alone also works.

When in doubt concerning the location of the exact acupuncture points, one can carpet-bomb the various areas, base of the skull, midback spinal and paraspinal areas, and knee creases, and it still works. Dr. Philibert suggests injecting the CVA angles bilaterally and down the edges of the inferior ribs as well as the supraspinus ligaments between the dorsal processes of the vertebrae in these levels to a depth of about 1 inch. He used lidocaine 0.25% (lidocaine 0.5% diluted with equal amounts of saline).

A Few Cases

A 60-year-old female with a history of kidney stones and acute CVA tenderness, and nausea with pain radiating into the groin was completely relieved of pain in the first few minutes after the first NT injection with Spascupreel. She didn't notice stones passing in her urine and has been asymptomatic for approximately 5 years.

A 60-year-old male with a many-year history of kidney stones was in a 2-week bout of pain medicated on Vicodin. His urologist said he had 9 stones and was in the ER every other night. His burning pain completely resolved after two NT treatments.

A 59-year-old female had been hospitalized in the ICU for 3 days with kidney stones 6 months earlier and now had recurring, debilitating kidney pain radiating to the groin that was 90% relieved after the first NT series and completely resolved with NT two days later.

Lithotripsy: No Walk in the Park.

We remember a patient prior to coming to us who relayed his history of lithotripsy several years previously for kidney stones. He experienced a renal artery laceration, which required transfusion of 6 units of blood and hospitalization for 6 weeks. ESWL (extracorporeal shock wave lithotripsy) has many side effects, including local bruising and damage to blood vessels of the kidney.[2,3] Kidney injury is dose dependent and can be severe, including internal bleeding and subcapsular hematomas.[4] Occasionally blood transfusions may be required and even lead to acute renal failure. Elderly patients have an increased incidence of acute onset hypertension and diabetes after ESWL.

Other Kidney-Bladder Distinct Meridian Uses

This acupuncture couplet has many other fabulous uses, including "problems of the descending colon, rectum, and anus, such as spastic colitis, inflammation of irritable bowel, diarrhea from intestinal malfunction or microbial infection, internal or external hemorrhoids, and anal fissures. It also addresses urinary tract disorders, from pyelonephritis and nephrolithiasis to chronic cystitis, prostate disease, urethritis, and incontinence. It can be activated to treat ovarian and uterine diseases, including complications of pelvic adhesions and pain on the posterior wall of the pelvis. Finally, the Kidney-Bladder distinct meridian couplet can be employed to treat coccygeal and deep axial back pain, especially low thoracic and lumbar pain."[5]

Last weekend a 60-year-old female staff member's son called to tell us that his mother was on the floor and unable to move for the last four or five hours secondary to 10 out of 10 pain in her left flank. On our arrival, her vital signs were normal and she had normal bowel sounds with no history of kidney stones and was 1 year post complete hysterectomy. She was extremely tender to palpation over the area. After we did the Kidney-Bladder distinct meridian areas and chased the pain down her left flank with more intradermal wheals of procaine and Spascupreel, her pain went down to a 2 out of 10 in about 15 minutes and remained low with gradual dissipation over the next several days. We also used Aconitum 200C (I think I'm gonna die) and Rescue Remedy (five-flower Bach Remedy). This situation could have created an extensive and expensive workup in the ER should she have chosen to go to the hospital, with much analgesic drugging.

I encourage you to try this approach in your practice. Patients really appreciate it.

Notes

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Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

The Role of Epigenetics in the Development of Allergies

Introduction

As allergy season is about to swing into full gear, some are starting to ask if allergies are heritable. Allergic diseases have increased dramatically over the past 25 years reaching epidemic proportions. But when does a person develop allergies? Is it in the womb or later in life? New research on the role of epigenetics is helping to answer this question. Epigenetics is the study of changes in certain characteristics that can be passed from one generation to the next without changing the DNA code itself. It has become apparent that changes in gene function, aside from those related to DNA mutations, are factors in numerous health conditions, including allergies.[1] Epigenetics explains why individuals with the same or similar DNA may have different health issues. Environmental factors are known to create epigenetic changes. These changes are also called epigenetic modifications. Low-dose chemical exposures affect genes that code for inflammation, asthma, obesity, cognitive development, hormone receptors, and allergies, among others. Prenatal and early childhood exposures increase the risk of allergies through epigenetics.[2]

Epigenetics

Most health conditions and disease involve changes in gene function. These changes might be caused by mechanisms other than changes in the deoxyribonucleic acid (DNA) sequence. The genome is programmed by the epigenome, which is composed of chromatin and a covalent modification of DNA by methylation. Epigenetics refers to the study of heritable changes in gene expression, caused by environmental modifications in a chromosome. Various chemicals in the environment are responsible for such changes. Epigenetic mechanisms mediate the effects of environmental exposures early in life, as well as lifelong environmental exposures and the development of disease later in life. The epigenetic program is encoded by DNA methylation, histone modifications, and noncoding RNAs. The epigenetic code provides flexibility of gene expression in response to environmental changes, allowing for adaptations across generations.[2] Epigenetic modifications may be inherited across multiple generations. Prenatal, parental, or grandparental exposures affect gene expression in offspring without altering DNA sequences.[3] These changes can be passed from generation to generation.

Changes in DNA methylation have been linked to seasonal allergies. Epigenetic regulation plays a key role in T-helper cell differentiation. Changes in DNA methylation patterns are observed at several key loci during this differentiation. Upregulation of IL4, IL5, and IL13 gene expression in Th2 cells is accompanied by a loss of DNA methylation and gain of permissive histone marks.[4] Allergies involve an inappropriate Th2 response to an allergen such as pollen, grass, or trees. Several known allergy, atopic, and asthma genes have been found to be susceptible to epigenetic regulation, including genes important to interferon (IFN)-γ, IL4, IL13, and IL17. [9]

The Allergy Link

In 2011, North and Ellis published a review of current literature on epigenetics and allergies. After reviewing both animal and human studies, they found evidence which indicates that transient environmental factors may have permanent effects on gene regulation and expression which potentially leads to the development of allergic disease.[5] Short-term exposure to environmental chemicals can have permanent effects on gene regulation and expression through epigenetic mechanisms. Histone modifications have been associated bronchial hyperresponsiveness and spasm in allergies and asthma. Animal studies have shown

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that a maternal diet rich in methyl donors can enhance susceptibility to allergic inflammation in the offspring, mediated through increased DNA methylation.[5] Animal studies have also implicated epigenetically modified dendritic cells in the transmission of allergic risk from mothers to offspring.[5] Prenatal exposures are a link to the development of allergies through epigenetic changes.

Recent research has linked air pollution and environmental tobacco smoke to seasonal allergies via epigenetic changes. Short-term exposure to particulate matter 10 (PM10) is associated with decreased methylation of the inducible nitric oxide synthase gene.[6] Nitric oxide plays a significant role in the regulation of the Th1/Th2 balance and contributes to the development of allergic diseases. Another study showed that exposure of adults to diesel and PM 2.5 over seven days was associated with DNA demethylation.[7] Again, these modifications can trigger allergies.

Medications can also trigger epigenetic modifications leading to allergic disease. Procainamide and hydralazine are two drugs that induce immune changes and autoimmune conditions through this mechanism. By affecting gene transcription, epigenetic changes can lead to changes in activation of promoter genes, ultimately affecting important signaling pathways such as NF-kB and apoptosis.[8] Procainamide is a cardiac drug known to induce autoimmunity, and hydralazine is used to treat hypertension.

Other environmental factors strengthen the link between epigenetic changes and allergies, especially when exposure occurs prenatally. Allergies and asthma are more likely to develop in children if the mother has allergies or asthma than if the father does.[9] This suggests the possibility of intrauterine programming. Prenatal smoking is linked to allergies, asthma, and atopic disease in offspring.[10] This raises the question, if allergies can be triggered prenatally or in utero, can they be reversed? Is it possible to utilize the information on epigenetic changes and allergies to reprogram the genome, offering a method of treatment or early intervention?

Reprogramming or Worsening?

Is there any evidence to support treatment or interventions other than avoiding the environmental triggers known to induce epigenetic changes? Based on previous published research finding that changes in DNA methylation resulting in aberrant gene transcription may enhance the risk of developing allergic airway disease, Hollinsworth and colleagues set out to see what happens with prenatal methyl donor supplementation. In mice, supplementation of the maternal diet with methyl donors was associated with greater airway allergic inflammation and IgE production in offspring and passed through generations. The mechanism was through epigenetic modifications regulating the differentiation of T lymphocytes.[11] However, diets rich in methyl donors did *not* significantly affect the airway disease phenotype of mice when exposed during either lactation or adulthood. There appears to be a period of vulnerability that is limited to in utero.[11] This study suggests that suppression of regulatory genes might contribute to enhanced allergic disease observed in animals exposed to dietary methyl donors.[11] Too much supplementation with methyl donors during pregnancy may have unexpected consequences, such as the development of allergic diseases. These consequences can affect generations of offspring. This animal study needs to be confirmed and duplicated in humans.

Other studies support that epigenetic changes are reversible. Nutrients can reverse or change epigenetic phenomena such as DNA methylation and histone modifications. They may do so either by directly inhibiting enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions.[12] Folate, vitamin B12, methionine, choline, and betaine can affect DNA methylation and histone methylation through altering 1-carbon metabolism. Biotin, niacin, and pantothenic acid also play important roles in histone modifications.[12] Nutritional epigenetics may be a way to prevent the developmental of diseases; however, it is very hard to delineate the precise effect of nutrients on each epigenetic modulation. Unintended side effects can occur.

Researchers are investigating many drugs that function through epigenetic mechanisms as a way to reverse modifications linked to disease. Azacitidine has been approved for use in the US to treat myelodysplastic syndrome, a blood disease that can progress to leukemia. The drug turns on genes that had been shut off by methylation.[13] Only 15% of those who take it receive benefit, and there are serious side effects of nausea, vomiting, anemia, and fever. It is difficult to predict which epigenetic modifications can be reversed with drugs, since they can turn on hundreds of genes while also turning off hundreds of others.

Summary

Epigenetics is the inheritance of changes occurring in gene expression that does not depend on changes to the DNA sequence. Most epigenetic changes occur as a result of DNA methylation or by modification of chromatin or histone proteins. Micro-RNAs have been discovered recently that may also effect changes in gene expression by their ability to act as inhibitors of transcription. Epigenetics could provide an explanation for well documented gene–environment interactions and the development of allergies. Epigenetic mechanisms are dynamic and potentially reversible with therapeutic intervention. Although the possibility of developing a treatment or discovering preventative measures of these diseases is being explored, current knowledge in nutritional epigenetics is limited.

Environmental Medicine

Further studies are needed to better understand the use of nutrients, bioactive food components, or drugs for maintaining our health and preventing diseases through modifiable epigenetic mechanisms. More research need to be done on the possible interventions related to epigenetic changes in the development of allergies.

Dr. Marchese is the author of *8 Weeks to Women's Wellness*. She maintains private practice in Phoenix, Arizona, and teaches gynecology at Southwest College of Naturopathic Medicine. She was named in *Phoenix* magazine's Top Doctor Issue as one of the top naturopathic physicians in Phoenix. Dr. Marchese is vice president of the Council on Naturopathic Medical Education and was recently appointed by Arizona Governor Jan Brewer to the State of Arizona Naturopathic Physicians Medical Board.

Notes

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APRIL 26: UNDERSTANDING, EVALUATING & ADDRESSING AUTOIMMUNE DISORDERS with William Kleber, DC, DABCI in Charlotte, North Carolina. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

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APRIL 28-29: INTERNATIONAL VITAMIN D CONFERENCE – Vitamin D, Sun and Human Health in Oslo, Norway. CONTACT: oslo2014.d-vit.eu/

APRIL 30: DR. JEFFERY BLAND BOOK SIGNING RECEPTION (1st of 10) for his new book *The Disease Delusion: Conquering the Causes of Illness for a Healthier, Longer and Happier Life* in New York City, New York. CONTACT: (800) 692-9400; www.metagenics.com/seminars

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MAY 8-10: AMERICAN OSTEOPATHIC ASSOCIATION OF PROLOTHERAPY REGENERATIVE MEDICINE (AOAPRM) PROLOTHERAPY & PRP CONFERENCE in Kansas City, Missouri. CONTACT: www.prolotherapycollege.com; LindaPavina@verizon.net

MAY 10: BUS TOUR OF MEXICAN CANCER CLINICS starts in Universal City, California. Also, **SEPTEMBER 3** and **SEPTEMBER 13**. CONTACT: 209-529-4697; frankcousineau@yahoo.com

MAY 10-11: BASTYR UNIVERSITY presents AURICULOTHERAPY ADVANCES IN PAIN & ADDICTION TREATMENTS in Kenmore, Washington (near Seattle). Also, **JUNE 6-7**. CONTACT: 425-602-3152; www.bastyr.edu/continuing-education

MAY 14-17: AMERICAN ACADEMY OF ANTI-AGING MEDICINE ANNUAL WORLD CONGRESS, FELLOWSHIP MODULES & BOARD CERTIFICATION EXAMS in Orlando, Florida. Also, **DECEMBER 10-13** in Las Vegas, Nevada. CONTACT: 888-997-0112; www.A4M.com

MAY 17: A HOLISTIC APPROACH TO OVERCOMING THYROID DISORDERS with David Brownstein, MD in Harrisburg, Pennsylvania. Also, **NOVEMBER 8** in San Antonio, Texas. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

MAY 17-18: CLINICAL APPLICATIONS AND ADVANCED TOPICS OF IV NUTRIENT THERAPIES IN ONCOLOGY in San Francisco, California. Also, **MAY 31-JUNE 1** in Chicago, Illinois. CONTACT: ivnutritionaltherapy.com/seminars/

MAY 28-30: METABOLISM, DIET AND DISEASE 2014: Cancer and Metabolism in Washington, D.C. CONTACT: www.metabolism-diet-and-disease.com

MAY 29-31: THE INSTITUTE FOR FUNCTIONAL MEDICINE ANNUAL INTERNATIONAL CONFERENCE-Functional Perspectives on Food and Nutrition: The Ultimate Upstream Medicine in San Francisco, California. CONTACT: https://www.functionalmedicine.org/AFMCP

MAY 30-JUNE 1: WORLDLINK MEDICAL presents ART OF CARING IN MEDICINE featuring Gregory Petersburg, D.O. in Tucson, Arizona. AMA PRA Category 1 credits. CONTACT: 888-222-2966; www.worldlinkmedical.com/courses/art-of-caring/

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MAY 30-JUNE 2: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. Topics: Dietary medicine and cancer; herbs for trauma and loss; environmental influences on autoimmunity; ADHD updates and options; targeting hypercoagulation for cancer. Early bird savings April 17. CONTACT: 541-482-3016; www.botanicalmedicine.org

MAY 31: NUTRITIONAL PERSPECTIVES ON NEUROLOGICAL DISORDERS with Court Vreeland, DC, DACNB in Boca Raton, Florida. Also, **JULY 12** in Austin, Texas; **SEPTEMBER 13** in Charlotte, North Carolina; **NOVEMBER 8** in Daytona Beach, Florida. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

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JUNE 7-8: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION SPRING CONFERENCE in Scottsdale, Arizona. CONTACT: 480-921-3088; www.AzNMA.org

JUNE 7-8: BASTYR UNIVERSITY presents ESOTERIC ACUPUNCTURE in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; www.bastyr.edu/continuing-education

JUNE 21-22: HEAVY METAL TOXICOLOGY: Chelation Therapy Including EDTA, DMPS, and oral chelation drugs in Phoenix, Arizona. For naturopathic, medical, nursing and medical student practitioners. CONTACT: ivnutritionaltherapy.com/seminars/

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JULY 17-21: ONDAMED 20 YEAR ANNIVERSARY in the Black Forest of Southern Germany. CONTACT: +1 845-534-0456/0, support@ondamed.net; www.ondamed.net

JULY 26: UNDERSTANDING, EVALUATING & ADDRESSING AUTOIMMUNE DISORDERS with William Kleber, DC, DABCI in Daytona Beach, Florida. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

AUGUST 30-SEPTEMBER 1: CANCER CONTROL SOCIETY presents its 42nd ANNUAL ALTERNATIVE THERAPIES CANCER CONVENTION @ Sheraton Universal in Universal City, California. **SEPTEMBER 2:** Doctors' Symposium. Mexican Cancer Clinic Tour on **SEPTEMBER 3 & 13**. CONTACT: 323-663-7801; www.cancercontrolsociety.com

SEPTEMBER 8-12: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE-A Five-Day Foundational Course in Functional Medicine in Scottsdale, Arizona. CONTACT: https://www.functionalmedicine.org/AFMCP

SEPTEMBER 10-13: AMERICAN ACADEMY OF ANTI-AGING MEDICINE FELLOWSHIP MODULES, BHRT SYMPOSIUM & BOARD CERTIFICATION EXAMS in Phoenix, Arizona. CONTACT: 888-997-0112; www.A4M.com

SEPTEMBER 15-17: PREVENTING OVERDIAGNOSIS @ Oxford University in Oxford, United Kingdom. CONTACT: www.preventingoverdiagnosis.net

SEPTEMBER 19-21: INTEGRATIVE MEDICINE FOR MENTAL HEALTH 5th ANNUAL CONFERENCE in San Antonio, Texas. Presented by Great Plains Laboratory. CONTACT: www.greatplainslaboratory.com/home/eng/kc_training.asp

SEPTEMBER 20: A DIFFERENT LOOK AT THYROID, CHOLESTEROL & DIABETES USING BLOOD CHEMISTRY with William Kleber, DC, DABCI in Naples, Florida. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

SEPTEMBER 21-26: KLINGHARDT ACADEMY WHIDBEY ISLAND RETREAT in Clinton, Washington. CONTACT: phone 908-899-1650; fax 908-542-0961; info@klinghardtacademy.com; www.klinghardtacademy.com

SEPTEMBER 26-28: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE CONFERENCE on PAIN in Dearborn Inn, Michigan. CONTACT: www.IntegrativeMedicineConference.com

OCTOBER 4: PERSPECTIVES ON NEUROLOGICAL DISORDERS with Court Vreeland, DC, DACNB in Bethesda, Maryland. Also, **DECEMBER 6** in Windsor Locks, Connecticut. CONTACT: Biotics Research, 800-231-5777; www.bioticsresearch.com

NOVEMBER 7-10: HEALTHY MEDICINE ACADEMY'S FOURTH ANNUAL INTEGRATIVE CANCER MEDICINE SYMPOSIUM in Phoenix, Arizona. Focus on clinical applications. Keynote Speaker: Keith Block, MD, the father of integrative oncology. 32.25 AMA; 36 ND CMEs; & more. CONTACT: (303) 499-1223; www.healthymedicineacademy.com; info@healthymedicineacademy.com.

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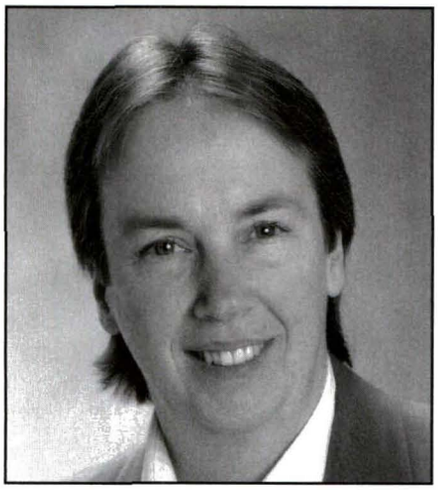

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Berberine Improves Lipids

A meta-analysis was done to evaluate the effectiveness and safety of berberine's influence on lipids. The researchers searched electronic databases through April 2012: Medline, Embase, the Cochrane Library, the China Hospital Knowledge Database, Wangfang, and other databases of ongoing clinical trials. The search included only clinical trials, in all languages. There were four categories of inclusion for these trials: (1) study subjects had to have received a berberine as a monopreparation or with other pharmaceutical products for 4 or more weeks; (2) the trials were randomized and controlled with either a parallel or crossover design; (3) berberine was the active treatment intervention; (4) the berberine data on its influence on lipids had to include triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). Those studies that used berberine containing herbs or extract instead of berberine as a single agent were excluded. One of two berberine formulations was used for all of the studies: 10 studies used berberine chloride tablets, 1 study used berberine chloride liposome capsules. Dosing ranged from 0.9 gm to 1.5 gm/day for 8 to 16 weeks. One study used 0.6 gm/day, and one study lasted a duration of 52 weeks.

Patients in the studies were primarily type 2 diabetics (4 studies), type 2 diabetics with hyperlipidemia (1 study), impaired glucose tolerance with hyperlipidemia (1 study), hyperlipidemia (2 studies), hypercholesterolemia (2 studies), and 1 study with polycystic ovarian syndrome patients plus insulin resistance. Eleven studies and a total of 874 patients met the inclusion criteria and were evaluated in the meta-analysis.

When the results were pooled for all 11 studies, berberine groups had a statistically significant reduction of TC, TG, LDL, and HDL when compared with the control groups. Berberine plus simvastatin also had a significant improvement in TC and TG although no effect on HDL. There was no reporting on whether these effects were large enough to reduce the risk of coronary heart disease. However, when pooling the results on LDL, the 25 mg/dL reduction was not only statistically significant compared with control, this is considered clinically meaningful based on Adult Treatment Panel III guidelines in that there is a 30% relative risk reduction for every 30 mg/dL reduction in LDL.

Comment: In this systematic review, the results were clinically meaningful, although only 2 of the 11 studies were considered high quality. In addition, one might need to consider whether the results would be different in a different ethnic group, and not exclusively Chinese individuals. Those things said, I will likely incorporate the use of berberine into my lipid and cardiovascular disease risk reduction management more than I have been doing. Once the dust settles a bit on the new lipid guidelines and treatment with statins, I can better incorporate the necessity for lipid management with lifestyle changes and botanical/nutrient supplements, all the while still focusing on the big picture of multiple mechanisms and their role in cardiovascular disease, not just the lipid-focused approach that has dominated conventional pharmaceutical primary and secondary prevention of cardiovascular disease.

Dong H, Zhao L, Lu F. The effects of berberine on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *Planta Med.* 2013;79(6):437–446.

Fish Oils in Perinatal Depression

This double-blind, randomized, controlled trial involved 126 pregnant women who were randomized to receive an EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), a DHA-rich fish oil (900 mg plus 180 mg EPA), or a soy oil placebo.

One hundred twenty-six pregnant women who were at risk for depression in early pregnancy were the final enrollment group in this study. Inclusion criteria included those with a past history of depression, a score of 9–19 on the Edinburgh Postnatal Depression Scale, singleton gestation, a maternal age of 18 years or older, and a gestational age of 12–20 weeks. Patients were excluded if they had a history of thrombophilia that required anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, or lifetime substance-dependency schizophrenia; were currently taking omega-3 fatty acid supplements; ate fish more two meals per week; or were on antidepressants. Eight of the 126 participants discontinued

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during the trial. One woman in the DHA-rich group had a second-trimester pregnancy loss. Seven were lost to follow-up. Thirty-nine women received EPA-rich fish oil, 38 DHA-rich fish oil, and 41 placebo. During the course of the study, there were 16 ongoing participants who discontinued the supplement prior to the final 6 to 8 weeks' postpartum evaluation.

Study subjects completed the Beck Depression Inventory (BDI) and Mini-International Neuropsychiatric interview at time of enrollment, 26 to 28 weeks, and 34 to 36 weeks as well as 6 to 8 weeks postpartum. Serum fatty acids of maternal blood and umbilical cord blood were also analyzed. There were no significant differences amongst the randomized groups in the change in the BDI scores between enrollment and the 34 to 36 weeks' gestation of the 6 to 8 weeks' postpartum visit. There were no differences in the mean BDI scores among the groups at entry or at any of the study visits. There were no statistically significant differences among the randomized groups and the number of women who started antidepressant medications or in dosing needs.

Omega-3 fish oil supplementation did significantly increase serum EPA in the EPA group and significantly increased serum DHA in the DHA-rich fish oil group. Serum DHA concentrations were inversely related to BDI scores at 34 to 36 weeks.

Supplementation with DHA-rich fish oil significantly lengthened gestation (40.4 weeks) compared with EPA at 39.1 weeks and placebo at 30.1 weeks, although this was not statistically significant.

Maternal DHA-rich fish oil supplementation significantly increased the umbilical cord DHA level, but umbilical cord serum EPA and DHA concentrations in infants born to the mothers who had received EPA-rich fish oil were not significantly different from the umbilical cord serum concentrations from infants born to mothers in the placebo group.

Comment: The findings of this study are in agreement with a 2010 *JAMA* study that also found no benefit for DHA-rich fish oil for prevention of depressive symptoms, although those women were not selected based on risks for postpartum depression.[1] The findings of the current study are also similar to those of a 2008 study, which also found no benefit for EPA-enriched fish oil for perinatal depression.[2] However, the current study is not consistent with another 2008 study for major depression during pregnancy and omega-3 fatty acids and two other studies done by Freeman et al. that did suggest benefit.[3-5] The primary concern with the current study is that it used lower doses of EPA/DHA than the positive studies. Another distinction is that this was a prevention study and not an intervention study in pregnant women with depression. While the current study found no benefit for EPA-rich or DHA-rich fish oil supplementation in the prevention during pregnancy and postpartum, it is noteworthy that DHA concentrations at 34 to 36 weeks were significantly predictive of depression at that same point in the pregnancy. In clinical practice, I recommend higher doses of EPA and DHA (e.g., >2000 mg EPA/>500 mg DHA for prevention and treatment of pregnancy-related and postpartum depression.

Mozurkewich E, Clinton C, Chilimigras J, et al. The Mothers, Omega-3 and Mental Health Study: a double-blind, randomized a controlled trial. *Am J Obstet Gynecol.* 2013;208:313. e1-9.

Omega-3 Fatty Acid Supplementation of Mothers and Allergy Programming for Infants

This was a secondary analysis of the Mothers, Omega-3, and Mental Health Study reported on above. Cord plasma specimens from 98 newborns were assayed for chemokines associated with T helper 2 and T helper 1 as well as exploring the mode of delivery on T helper 2/T helper 1 ratios. The cord plasma specimens from the 98 newborns were taken from the 126 women who received the EPA enriched (1060 mg EPA plus 274 mg DHA) or DHA enriched (900 mg DHA plus 180 mg EPA) or placebo over the course of the pregnancy.

Stored samples were analyzed for the chemokines of interest. Chemokine assays were performed on maternal venous blood samples drawn at enrollment between 12 and 20 weeks' gestation and after supplementation at 34 to 36 weeks' gestation. Umbilical cord blood was collected at delivery from 98 neonates whose mothers were in the trial.

The key finding was that both omega-3 supplementation groups were associated with a modulation of fetal Th2/Th1 balance in cord blood. No differences in maternal chemokines were detected at baseline or after the supplementation, and there were no significant differences between the placebo, EPA-rich, and DHA-rich groups.

Comment: While the current study does not have any clinical data on allergic diseases in these infants, the results do suggest that the omega-3 fatty acid supplementation modulates the fetal immune response and a potential positive influence on allergic diseases in children born to mothers who supplement with adequate EPA/DHA. Previous epidemiologic studies have found that the maternal diet and mode of delivery; for example, cesarean, may significantly increase the risk for allergic diseases in the children of those deliveries due at least in part to the Th2/Th1 ratios at birth.

Romero V, Someres E, Stolberg V, et al. Developmental programming for allergy: a secondary analysis of the Mothers, Omega-3 and Mental Health Study. *Am J Obstet Gynecol.* 2013;208:316. e1-6.

Notes

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3. Su K, Huang S, Chiu T, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2008;69:644–651.
4. Freeman M, Hibbeln J, Wisner K, et al. An open trial of omega-3 fatty acids for depression in pregnancy. *Acta Neuropsychiatrica.* 2006;18:21–24.
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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 28 years; and is the medical director of the clinic A Woman's Time in Portland, Oregon, and director of research and development for Vitanica, a supplement company for women. She is also a nationally recognized author, speaker, educator, researcher, and clinician.

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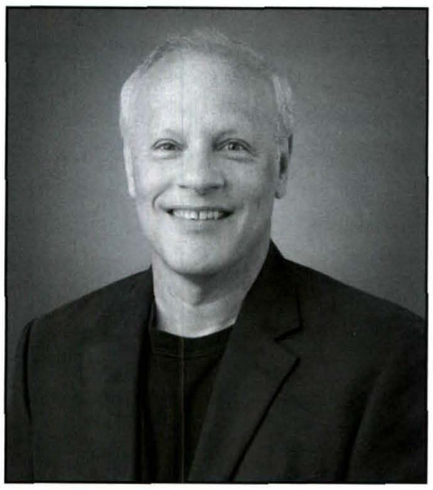

Dr. Wright Does It Again: D-Mannose for UTI Prophylaxis Validated in a Clinical Trial

I have been privileged to have been associated with Jonathan Wright, MD, since 1978. At that time he was offering a "fellowship" for medical students, and I was given the opportunity to spend a month in his clinic, learning from him and from the large collection of medical journal articles on nutritional therapy that he had collected over the years. Five years later, we began coteaching seminars on how to incorporate nutritional therapy into medical practice, and we have continued to do so for 30 years.

One of the things that have impressed me about Dr. Wright is his ability to discover or develop or invent new therapies that turn out to be effective. He was the first doctor in the US to use bioidentical estrogen-replacement therapy (estrone, estradiol, and estriol), and one of the first to use DHEA in clinical practice. He also pioneered the use of selenium and vitamin E as a treatment for Osgood-Schlatter's disease.

Some 20 years ago, Dr. Wright began using D-mannose (a sugar structurally similar to glucose) to prevent and treat urinary tract infections, based on in vitro reports that it prevents uropathogenic *Escherichia coli* from adhering to the epithelial cells of the genitourinary tract. Since then he has administered D-mannose to more than 200 patients. In his experience, this treatment has an efficacy rate of 85% to 90%. Hes has found that in addition to being an effective treatment for UTIs, D-mannose can prevent postintercourse UTIs and is also effective for prophylaxis in women who are prone to recurrent UTIs. For treatment of UTIs, he recommends a dosage of 1 teaspoonful (about 2 g) for adults and ½ to 1 teaspoonful for children, dissolved in a glass of water or juice and repeated every 2 to 3 hours. Treatment should be continued for 2 to 3 days after symptoms have disappeared. For preventing recurrent infections, patients should start with the dosages listed above, and then reduce the dose if possible. For prevention of postintercourse UTIs, the recommended dosage is 1 tablespoonful 1 hour prior to intercourse and again immediately afterwards.[1] D-mannose is not effective for UTIs caused by organisms other than *E. coli*.

Hundreds of practitioners are now using D-mannose because of the writings and teachings of Dr. Wright, and informal surveys that I have conducted at medical conferences reveal that these practitioners generally concur with Wright's observations. D-mannose is now widely available in natural food stores and on the Internet. However, while it appears to be quite effective, the evidence supporting its use has been entirely anecdotal. Now, finally, a randomized controlled trial has been published that confirms the efficacy of this treatment.

In the new study, 308 women with an acute UTI and a history of recurrent UTIs were treated with ciprofloxacin (500 mg twice a day for 1 week) and then randomly assigned to receive 2 g per day of D-mannose, 50 mg of nitrofurantoin once a day, or no prophylaxis for 6 months.[2] Women with urinary tract anomalies, interstitial cystitis, or diabetes, and those who were pregnant or taking hormone therapy or contraceptives were excluded. During the study, 98 women (32%) had a recurrent UTI. The recurrence rate was significantly lower in the groups that received D-mannose (15%) and nitrofurantoin (20%)

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Editorial

than in the group that did not receive prophylaxis. The recurrence rate did not differ significantly between the D-mannose and nitrofurantoin groups. The incidence of side effects was significantly lower in the D-mannose group than in the nitrofurantoin group. Eight percent of patients receiving D-mannose experienced diarrhea, which did not require discontinuation of treatment.

The discovery of the D-mannose as a treatment for UTIs was an important medical advance, although its mechanism of action may be different than that initially hypothesized by Wright. D-mannose is absorbed intact into the blood, but there are no data indicating what proportion of an orally administered dose is excreted unchanged in the urine.[3] Even if 100% of the recommended oral dose of D-mannose were excreted in the urine, the average urinary mannose concentration would be less than half the concentration that decreased bacteriuria by 90% in rats. Moreover, once *E. coli* has adhered to the bladder wall, one could not necessarily expect that free mannose in the urine would successfully detach it from its cellular binding sites. Another possible explanation for the efficacy of D-mannose is its relationship to Tamm-Horsfall protein. This glycoprotein, produced by renal cells and excreted in the urine, plays a key role in the body's defense against UTIs. Tamm-Horsfall protein contains a large number of high-mannose structures, which appear to account for its infection-fighting activity.[4] It is possible that orally administered D-mannose works primarily by facilitating the synthesis or promoting the activation of Tamm-Horsfall protein. Regardless of the mechanism, thousands of people are grateful to Dr. Wright for discovering the benefits of D-mannose and telling the world about it.

Alan R. Gaby, MD

Notes

1. Wright JV, Lenard L. *D-Mannose and Bladder Infection*. Auburn, WA: Dragon Art; 2001. Additional information regarding the use of D-mannose was obtained in a personal communication from Wright JV; September 10, 2008.
2. Altarac S, Papes D. Use of D-mannose in prophylaxis of recurrent urinary tract infections (UTIs) in women. *BJU Int*. 2014;113:9–10.
3. Alton G et al. Oral ingestion of mannose elevates blood mannose levels: a first step toward a potential therapy for carbohydrate-deficient glycoprotein syndrome type I. *Biochem Mol Med*. 1997;60:127–133.
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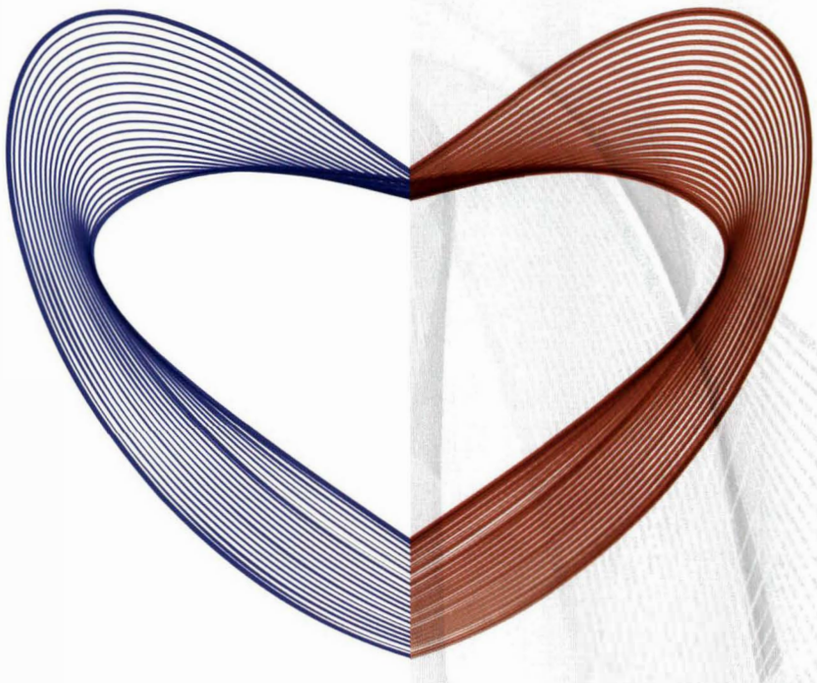

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