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*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.
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Discerning the Mauve Factor, Part 2

This painting was inspired by a Sumerian creation myth dating earlier than 5000 BCE and depicts the god Enki, often associated with the stag, and Lady Ki, the earth. Together this divine pair created what historians refer to as the Fertile Crescent, a place now known as Iraq, Iran, Syria, and Turkey. Below is a brief explanation of this painting, written as if spoken by master magician Enki, patron god of artisans, also known as Sweet Water.

"From the very beginning, when my beloved and I first arrived at this place, we saw possibility. Creatrix and creator, together we fashioned clay prototypes for all manner of living beings. I assisting, Ki birthed our plant children and the world became a living tapestry. I then bathed her weary body with fresh flowing waters and on a whim, to see her smile, filled these with dancing fish. My Lady Ki: fertility itself, wherever she steps there springs forth abundance! We two, the Great Stag and Mother of Earth, populated the earth with all that runs and flies. Ki’s supple energy is replicated in all green and fecund things, and to this day everywhere I look, I see her face."

Ki and Enki Rest After Their Labors. Watercolor and pencil, Helena Nelson-Reed.

Ki and Enki is available as a fine art print. For information on this and other works, please contact Helena at hnelsonreed@gmail.com or visit her website, www.helenanelsonreed.com.
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I discovered this product at a medical conference, and was intrigued by the research. One of the published studies reported that patients experienced a 40% decrease in fatigue(1) in eight weeks. The product is formulated to deliver a stabilized unique phospholipid matrix (this is what composes the mitochondrial membranes), wrapped in pre and probiotics as well as Mitochondrial Pro Regulator™ to optimize mitochondrial function, Krebs Cycle Glucose Absorb™ to propel the burning of glucose, creating energy and removal of excess ammonia which can cause fatigue, and RN Fatty Acid Metabolizer™ to maximize ATP production by regulating fatty acid buildup which, if left unchecked reduces mitochondrial function and increases cellular toxins. Normally, cells produce and repair their own mitochondrial membranes. However, these membranes may become compromised during long-term illness or interestingly, intense physical exercise by healthy individuals. This product helps the body help itself. By improving cell membrane potential, nutrients are better able to enter the cells for greater ATP fuel production, toxin removal is improved and oxidative stress is reduced.

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I actually tested the blood level of a patient on this product versus another well-known CoQ10. The patient using CoQ10 Power™ had three times the CoQ10 in the blood than the other product. As I have come to expect from Researched Nutritionals, the raw material is of the highest quality and is imported from Japan.

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- **Healthy Cell GTP™** - Potent extracts of green tea and pomegranate to promote normal cell division and containing high levels of crucial antioxidants.
- **Plus an integrated blend of folic acid, vitamin B-12, zinc, and selenium to strengthen immune function, promote normal cell growth and boost antioxidant levels.**

I believe a healthy energy level and a fortified immune system are essential to good health.

Best Regards,
Dr. B.
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DOES DEMENTIA EXIST? DISPELLING THE MYTH

Mark A. Hyman, MD

Mark A. Hyman, MD, is the editor in chief of Alternative Therapies in Health and Medicine. (Altern Ther Health Med. 2008;14(2):10-12.)

The great enemy of truth is very often not the lie—deliberate, contrived and dishonest—but the myth—persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought.

—John F. Kennedy

Obesity is obvious. Just look around the American landscape. But memory loss and cognitive decline is invisible—and more fearsome. Alzheimer’s disease will affect 30% (and some experts say 50%) of people over 85 years old, which is the fastest growing segment of the population. The prevalence of Alzheimer’s is expected to increase 3-fold by 2050 affecting 14 million people, at an annual cost at $83.9 billion to our healthcare system and society, which doesn’t even begin to account for the untold suffering on families and caregivers. It is now the seventh leading cause of death.

With Alzheimer’s we are facing a global problem. It is projected to increase 285% in North America, 534% in South America, 476% in Africa, and 497% in Asia by 2050. Even small progress in preventing the disease and slowing its progression will have a profound impact on the personal and financial costs we will bear.

If we want to do something other than provide palliative care, we must ask certain questions. What is dementia? What causes it? Is it uniformly the same disease or the heterogeneous manifestation of multiple genetic and environmental insults? Can it be prevented? Can it be slowed, stopped, or even cured? And why are we seeing growths of epidemic proportions of the incidence of cognitive dysfunction, mild cognitive impairment (MCI), and dementia?

Conventionally dementia falls into 2 main categories—Alzheimer’s and vascular dementia, with many other minor variations. Therapy is limited to 2 main categories of medication—acetylcholinesterase inhibitors and NMDA (N-methyl D-aspartate) receptor antagonists, neither of which addresses the causes of dementia and both of which are marginally effective (if at all) and have significant side effects. New treatments such as vaccines are on the horizon.

Emerging research indicates that inflammation, oxidative stress, insulin resistance, and mitochondrial dysfunction are key mediators of brain degeneration. But rarely is the question explored as to why these processes occur. What are the proximal causes? Is there another clinical model for preventing, treating, and even reversing cognitive decline and dementia? Even more, mounting research suggests that loss of cognitive function is not a homogeneous process and that Alzheimer’s or dementia is not a single disorder but a common clinical manifestation of disordered neuronal function arising from a multitude of genetic, environmental, and lifestyle factors unique to each individual. Even if large-scale system-based clinical trials are yet to be done—or difficult to do—if we can assemble existing data into safe lifestyle-based and nutritional interventions for optimizing brain function, then we might hold back the tsunami of broken brains and broken lives we face.

HEALING THE MIND AND REVERSING DEMENTIA: IS IT POSSIBLE?

New research suggests that focusing on the “disease” called dementia and finding drugs to modify downstream effects of brain injury such as insufficiency of acetylcholine misses the opportunity to address the real problems. In fact, “dementia” does not exist but is simply a common collection of symptoms that explain nothing about the underlying etiology or pathophysiology. These include inflammation, oxidative stress, insulin resistance and other hormonal dysregulation, mitochondrial dysfunction, nutritional deficiency, and toxic injury. The question is not how to treat dementia, because it is not a single disorder, but how to find the underlying reasons for our broken brains and how to fix them.

The cognitive dysfunction we call dementia is simply the way the body expresses injury to a myriad of insults that can be quite different from person to person. No 2 “dementias” are exactly alike. But how do we apply molecular personalized genomic medicine to such a complex disorder?

The answer is quite simple. Ample science lays out the patterns of dysfunction in dementia and, to a great degree, most of the precipitating causes. Then our individual genetic differences and predispositions set us up for biological breakdown from the same few common insults—toxins such as mercury, digestive imbalances, nutritional deficiencies or excesses, stress, allergens, infections. These in turn, lead to the altered physiological processes we see in the “dementias”—inflammation, oxidative stress, mitochondrial dysfunction, and insulin resistance.

We have to think about individuals, not diseases. In medicine our differences (genetic predispositions, environmental exposures, diets, and stresses) are more important than our similarities. Sometimes the practice of medicine lags behind the science, and sometimes the practice gets ahead of the science. Genetic testing
puts us squarely in the middle of that dilemma.

We are at a crossroads where the old ideas we have about disease and diagnosis become less meaningful as we understand more and more about the importance of individual differences in determining illness. This is a time when personalized medicine will replace medicine based on diagnosis and disease. In fact, disease and diagnosis as we know it (ICD-9 classification of diseases) will soon be an obsolete concept, an artifact of medical history like bloodletting or phrenology (the art of diagnosis based on the shape of your skull, popular in the 19th century).

AN “N” OF 1: REVERSING DEMENTIA

As a medical student, I participated in a public health research project in a remote Nepalese village. In exchange for the villagers’ help, we offered an improvised outdoor medical clinic. One man brought his mother to our clinic after carrying her on his back for 10 days through the Himalayas. I asked how we could help. He said his mother was blind. She had cataracts. There was nothing we could do.

That is how I felt about my patients with dementia until I met “George.” George presented with dementia. His story is an example of how treating a person—not a disease—leads to improved clinical outcomes; how environmental influences on genetic predispositions—mostly mercury exposure in this case—can lead to any number of diseases depending on individual genetic variations.

George presented with a diagnosis of dementia after a comprehensive neurological evaluation including neuropsychological testing, MRI (magnetic resonance imaging), MRA (magnetic resonance angiography), and SPECT (single-photon emission computed tomography) scanning. When he came with his wife to see me, he could no longer manage his business affairs, had become increasingly unable to function at home, and had to withdraw from family and social relationships.

HOW THE ENVIRONMENT AFFECTS YOUR GENES: A CASE OF MERCURY POISONING

Chronic diseases, like Alzheimer’s, cardiovascular disease, or cancer are usually multi-gene disorders. It is not 1 gene but the interaction between many genes, their variations or single nucleotide polymorphisms (SNPs), and the environment that puts someone at risk for a chronic disease such as dementia. That is why we will never find “the” gene for Alzheimer’s—or heart disease, cancer, autism, or depression.

In the case of George, whose mind and life were evaporating, I looked deeply into his genes and the biochemistry his genes controlled and found places we could improve things. He was homozygous for apo E4, a high-risk gene for Alzheimer’s disease that also predisposes to dyslipidemia and impaired heavy metal detoxification from the brain.1

A 6-hour DMPS provocation challenge test for heavy metals* revealed mercury of 350 mg/g creatinine (normal < 3 mg/g creatinine). Sources of mercury include vaporization of dental fillings or environmental exposures from tuna fish or air pollution.6 George lived his life in an industrial area with large coal burning plants and had many dental amalgams.7 Mercury toxicity is a potent neurotoxin linked to many neurological disorders including dementia.8

In one study of 465 patients with chronic mercury toxicity, 32% had severe fatigue, 88% had memory loss, and almost 30% had depression. These symptoms and mercury poisoning were much more common in people with the apo E4 gene. Removal of amalgam fillings combined with a mercury detoxification program resulted in significant symptom reduction.9

*Blood levels of mercury only reflect recent exposure from pollution or fish consumption, but a provocation test identifies total body burden of mercury. Studies have found that using DMPS increases mercury excretion from 3- to 107-fold. The chelating agents or drugs, DMPS and DMSA, are both used to treat heavy metal toxicity.
PERSONALIZED MEDICINE: A CURRENT REALITY OR FUTURE POSSIBILITY?

Based on George’s unique genotype and his phenotypic expression (elevated body burden of mercury, hyperlipidemia, insulin resistance, hyperhomocysteinemia, low glutathione, and impaired detoxification), a therapeutic plan was developed to address his entire systemic dysfunction. George also had a 30-year history of irritable and inflammatory bowel diseases, which has been linked to dementia and other neuropathologies.18

The single gene, single disease, single drug model is inappropriate for complex multi-gene systemic disorders with common manifestations but differing etiologies such as dementia. The components of his therapeutic plan were designed to remove toxic triggers (mercury, poor diet, dysbiosis), while optimizing nutrient-regulated gene expression. Doing just one thing wouldn’t help George. Treatment required addressing all the imbalances, the causative factors, and their effects systematically.

Treatment included careful mercury detoxification including safe amalgam removal and chelation. Phytoneutrients and nutrients that upregulate glutathione, including cruciferous vegetables such as kale, watercress, and cilantro; herbs such as milk thistle; nutrients such as selenium and zinc, were added to his diet. His hyperlipidemia and insulin resistance were managed with a low glycemic load, plant-based high-fiber whole foods, organic diet, and exercise.

To further improve his genetic limitations in methylation and sulfation, he was treated with high doses of MTHF (methyl-tetrahydrofolate),22 methylcobalamin,22 and B6. To address his gut inflammation, food allergens were eliminated, small bowel bacterial overgrowth was treated, and enzymes and probiotics were replaced. Additional basic nutritional support, including a multi-vitamin and omega 3 fatty acids,22 was provided.

After a year of aggressive therapy that was matched to his quirky genes and biochemistry—not his diagnosis—George had a remarkable and dramatic recovery. Before I saw him, he could not manage his business nor did his grandchildren want to be around him. After matching his treatment to his genes, he was again to function able, and his grandchildren loved being with him.

Although this area of genetic testing and nutrigenomics is new and more research is needed to help us refine our understanding and treatment, there are ways to look through new doors into an entirely new era of medicine—one that no longer focuses on the disease but on the person and his or her uniqueness. Widespread genetic testing is not ready for primetime, but it can be a helpful guide in understanding the origins and the risks of some chronic illnesses. But we have to recognize that it is the interplay of many genes interacting with the environment that determines our health. What we do know is that there is no single gene for Alzheimer’s—or autism, depression, heart disease, or cancer. In fact, those diseases, as single homogenous, uniform conditions, do not exist. We must give up that myth.

Instead, there are common variations in the symphony of our gene patterns that are integral to many chronic diseases. These patterns vary from person to person and are highly influenced by diet, stress, infections, allergens, and toxins.

The time has come to focus on systems approaches to complex systems disorders. Treatment based on mechanism, genetics, biochemistry, and physiology will supplant diagnosis-based treatment. Clinicians can begin to navigate with a different map for the territory of illness than the one we received in our training and in the process can become re-enchanted with medicine and the possibility of healing where there was none.
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Dr. LaVonne Veatch Goodman, M.D.
Does Complementary and Alternative Medicine Represent Only Placebo Therapies?

Jeffrey Bland, PhD, FACN, FACB

Guest Editorial

Complementary and alternative medicine (CAM) is “something you heard about from your hairdresser, who thinks she saw it on Oprah—a category that . . . includes acupuncture, homeopathy, healing magnets and assorted herbs and supplements.” This is a quote from Jerry Adler’s editorial in the December 1, 2007, issue of Newsweek titled, “A Big Dose of Skepticism.” The editorial represents a strong “shot across the bow” of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health as well as the tens of thousands of licensed CAM practitioners and millions of their patients who regularly employ what have been termed “CAM therapies.”

Mr Adler states that his 2008 resolution as a medical writer is to “not report on any new treatments for anything, unless they were tested in large, randomized, placebo-controlled, double-blind clinical trials published in high-quality peer-reviewed medical journals.” He takes his lead in this advocacy from the recent book, Snake Oil Science: The Truth About Complementary and Alternative Medicine by R. Barker Bausell, PhD. In essence, Bausell makes a strong case using his background as a former director of research for the University of Maryland’s Center of Complementary and Alternative Medicine that all CAM therapies have an impact on health only by placebo-related effects. He bases his conclusions on the efficacy of CAM therapies on the following 5 criteria:

1. Studies of CAM therapies that show benefit beyond placebo effects have not been done well, whereas studies of CAM therapies that are methodologically sound have not demonstrated benefit beyond placebo.
2. Scientists and clinicians engaged in either the administration or study of CAM therapies have an inherent bias in support of the positive nature of the therapies, and therefore their conclusions are suspect.
3. Scientists and clinicians associated with CAM therapies do not understand methodological issues in the science of clinical trials such as the placebo effect, attrition/drop-out, the natural history of the disease in question, the Hawthorne effect, regression to the mean, or statistical methods of analysis.
4. No scientific mechanism of action for the validity of CAM therapies has been proven beyond that of the known mechanism of action of the placebo effect.
5. There is a lack of understanding of the concept of parsimony (ie, Occam’s razor) that results in unusual and unproven mechanisms beyond placebo effect to be ascribed to CAM therapies.

In support of his contention that these 5 criteria define the limitations of CAM studies, Bausell provides evidence using the Cochrane Collaboration database of 98 randomized, controlled CAM studies published in 4 top-tier, peer-reviewed journals: The New England Journal of Medicine, JAMA, Archives of Internal Medicine, and the Annals of Internal Medicine. These studies include acupuncture, herbal therapies, chelation therapy, traditional Chinese medicine (TCM), electrical stimulation techniques, hypnotherapy, homeopathy, intercessory prayer, massage, meditation, manipulative therapies, ultrasound, and nutritional supplements such as glucosamine. As he applies his criteria to the validity of these studies he shows that only 5% of the 98 published studies demonstrate positive outcomes beyond that of placebo. It is this analysis that leads to his conclusion that “after initiating [what appears to be a successful CAM] therapy, if you begin to experience some fall-off in its benefits, discuss the situation immediately with your therapist. Most experienced CAM therapists will have a menu of new strategies capable of initiating a new round of placebo effects.”

What is wrong with this analysis of the efficacy of CAM therapies? The analysis is based on well-founded concerns from an expert in scientific methodology. It would seem that Bausell has offered a fait accompli that wipes away thousands of years of history associated with the purported clinical success of many traditional healing methods with the stroke of one scientific eraser.

But there is much more to the story than that which is told. First of all, he has seemingly lumped all of what is considered non-traditional medical intervention under the rubric of CAM. He has selectively chosen issues in the history of science to support his hypothesis that there is no basis of a clinical benefit for any CAM therapy (which many readers might interpret as “non-pharmacological therapies”) beyond that of placebo. The implication of Bausell’s argument is that the success that was witnessed with the development in the 1930s of antibiotic therapy ushered in the era of successful, non-placebo therapies’ that, unlike CAM therapies, had demonstrable effects beyond that of placebo. With regard to the
necessity of conducting large randomized clinical trials to determine non-placebo effects of a specific therapy, it is interesting to note that many accepted surgical procedures have not been tested by randomized, placebo-controlled trials. They are, however, considered standards of care based on agreement among trained medical professionals that they are efficacious.7

Also interesting is Bausell’s contention that it is essential to know the mechanism of action of a specific therapeutic intervention when it is well known that many of the pharmaceutical preparations approved for use by the US Food and Drug Administration do not have known mechanisms of action. The definitive criteria that establish the safety and efficacy of any therapy may be a little more complicated than Bausell’s analysis implies.

There is another important limitation of using the randomized, placebo-controlled trial as the only criterion for determining the non-placebo value of a therapy. The randomized, placebo-controlled clinical trial favors the evaluation of an intervention that can be easily blinded and placebo-controlled. As such, it is an excellent methodology to evaluate the effect of 1 pill tested against 1 clinical endpoint—for example a new-to-nature angiotensin-converting enzyme inhibitor for systolic and diastolic blood pressure compared to an identical-looking placebo. This methodology, however, is not as easily applied when one wants to study the effect of a CAM therapy involving specific diet or lifestyle intervention on blood pressure. Diet and lifestyle interventions are impossible to completely blind and therefore are more susceptible to issues related to the Hawthorne effect, compliance, dropout, or the placebo effect.

The issue of the limitations of control of dietary intervention trials was discussed in a recent review describing the inter-individual variation of response that occurs in dietary studies and the need for managing genetic heterogeneity with large study groups and specific dietary subgroup analysis.7 This criticism can be applied to important studies such as the Dietary Approach to Stopping Hypertension (DASH). These studies demonstrated clinical validity of the effect diet and lifestyle have on hypertension but did not fulfill Bausell’s criteria of an acceptable, randomized, placebo-controlled trial.10,11 In the end, the well-designed study of a pharmaceutical product for hypertension has far fewer methodological issues confounding its results than do the diet-and-lifestyle intervention studies.12,13

Beyond the obvious methodological challenge of how to blind and develop appropriate placebos for CAM intervention trials is another thorny issue. How long does it take to demonstrate true improved patient outcome in a clinical trial? Most clinical intervention trials evaluating the effect of a new therapeutic agent for the management of a chronic health problem will be of a year’s duration at most. It is assumed that at the end of this period of time the safety and effectiveness of the agent has been “proven.” But what if this agent is applied in clinical practice for a much longer duration than the 1 year it was studied? Many patients with a chronic disease have their therapies applied indefinitely, as is the case with type 2 diabetes, osteoarthritis pain and disability, chronic digestive problems such as esophageal reflux disease, chronic depression, benign prostatic hypertrophy, hyperlipidemias, and hypertension.14,15 In these cases the true safety and effectiveness of the therapy that had been proven through the administration of a successful short-term randomized, placebo-controlled trial might in the longer term prove to either not improve outcome or even cause serious adverse effects. An example is the recent voluntary recall of the selective COX-2 inhibitor Rofecoxib by Merck & Co (Whitehouse Station, New Jersey) due to the number of adverse drug reactions that occurred after patients had been taking the drug for an extended period of time.16,17 It wasn’t that the drug had not been proven to be safe and effective through multiple randomized, placebo-controlled trials—rather, the adverse drug reactions occurred when patients took the drug for a period of time that was longer than the duration of the clinical trials.

A CAM treatment often is based on a much longer historical perspective of safe use in indigenous cultures.18,19 It may not “measure up” in terms of outcome from a short-term placebo-controlled trial, but it may actually provide for both a safer and more effective outcome in the longer term. No long-term, head-to-head outcome studies have been done to compare the safety and effectiveness of specific CAM therapies to those of pharmaceutically based therapies.20,21 However, population studies of various diet and lifestyle CAM therapies have shown significant improvements in health outcomes when compared to populations that have not adopted these habits.22,23 The recent HALE (Healthy Aging Longitudinal Study in Europe) project, a 10-year study of health outcomes in individuals aged 70 to 90 years who elected to consume a Mediterranean diet compared to an age- and gender-matched control group in the same countries who consumed their traditional European diet, illustrates this concept.24 The study reported that “among individuals aged 70 to 90 years, adherance to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-cause mortality and cause-specific mortality.”25(p1433) Although this study doesn’t fulfill the Bausell criteria of a randomized, placebo-controlled trial, it was published in a peer-reviewed, tier-one journal, and the results have potentially significant implications on health outcomes of an aging population. As Ivan Ilich said in his landmark book Medical Nemesis26 and as suggested by the HALE study, the big breakthroughs in health have not occurred through agents developed by the application of the randomized controlled clinical trial to develop new medicines but rather through the effective application of nutrition, sanitation, and hygiene, all of which were considered “CAM therapies” in their time.

The question that emerges from Bausell’s interpretation of CAM therapies is whether the randomized clinical trial is the appropriate methodology to address the most important questions concerning our health where chronic disease is the dominant form of disease in the developed world.27 What is emerging is a different model for evaluating a therapy’s safety and effectiveness that is born out of the developing algorithms of systems biology.28,29 It uses multivariate, non-parametric statistical methods of analysis of complex data sets. Rather than constructing the experiment to hold all variables constant except the clinical endpoint that is to be
studied, this model allows the participants to engage in real-world activities of daily living and then determines how the captured complex data set clusters into patterns of significant outcome.2,20 Bausell’s questioning of the non-placebo validity of all CAM therapies is built on an old model of statistics. It is through the computing power of the 21st century and new technology that pattern recognition and cluster analysis of complex data sets can be routinely accomplished.

Work that is being done on the analysis of complex biological systems at places such as the Institute for Systems Biology in Seattle, Washington, has presented an opportunity for new experimental methodologies to be employed in clinical studies.21 These new methods of analysis don’t suffer the “one agent for one outcome” bias of the randomized, placebo-controlled clinical trial. The systems biology approach to medicine is now being seriously discussed as part of the development of an integrated biological approach to healthcare.22 The Institute for Functional Medicine recently published the Textbook of Functional Medicine, which describes a clinical approach to applying systems biology to the management of chronic disease.23

The clinical model described in the textbook is built on a foundation of evidence from not only randomized, controlled clinical trials but also studies published from epidemiology, meta-analyses, case-controlled studies, basic science discoveries, and complex data set analyses. The functional medicine approach to chronic disease represents a new paradigm in healthcare that moves beyond the limitations of CAM described by Bausell.

We are witnessing a new era in which it might be said that we are “moving back to the future.” The move back is to explore what makes the greatest impact on improving health outcomes in a society burdened with the rising incidence of chronic disease from a historical perspective. The future holds the development of new experimental methods of designing studies that can better address complexity within human populations and the computing and statistical methodologies to bring clarity from confusion.14,26

It is certainly true that all interventions are “tainted” by methodological issues such as the placebo effect. Some therapies have a much greater likelihood of a strong placebo effect than others, such as those for chronic pain. It is also true that some therapies are much more difficult to separate methodologically from that of the placebo effect. This is the case with a number of CAM therapies in that it may be virtually impossible to completely blind the participants or the practitioners or provide a suitable placebo. Using the new experimental methods that are based on complexity theory and systems biology and the statistical methods that support them, we will be better able to address the long-term safety and efficacy of many CAM therapies. It is through this work that studies will help answer the question of which CAM therapies work via placebo effect and which therapies will aid us in fighting chronic disease and infirmity.26

REFERENCES
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From 2000 to 2004 I had the pleasure and opportunity to write a regular column entitled "Progress Notes in CAM Education" for this journal. At the time, exciting new things were happening in the academic world with the evolution of a wide range of educational initiatives in complementary and alternative medicine (CAM) education. I interviewed educators and documented their projects, curricular changes, institutional and cultural challenges, evaluation efforts, feedback from learners, funding issues, time and effort, faculty development, and more. A mid-trajectory summary article was published that reviewed the major trends in CAM education at that time.1 It was during an era when the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH) was investing more than $21 million in a series of educational enhancement grants in CAM education and many of those columns summarized work that was just starting or underway across the country.

We have come a long way since then. In October 2007, Academic Medicine: Journal of the Association of American Medical Colleges, the premier journal for medical educators, published a theme issue comprised of 9 papers summarizing the outcomes, methods, processes, evaluation, and impact of the NCCAM-funded projects.3,4 This was a high watermark for the field in that it presented the broad academic medicine community with a solid showing of the state-of-the-art education in CAM and integrative medicine (IM). While any one publication or even a theme issue rarely makes a tectonic shift in the methods and culture of academia, the presence of such a theme issue offers us hope that gradual acceptance and integration of the role of CAM/IM training is occurring and that sustainable change is upon us.1 Indeed, surveys of medical schools continue to show that nearly all of them have some offerings in this area and also that board examinations are increasingly quizzing students on this content.

It is, of course, a positive step that ATHM continues to print new research on CAM/IM education, as in this issue. Our colleague Peter Wayne is an established, well-respected CAM educator and researcher. I found his report of developing research capacity at the New England School of Acupuncture in collaboration with Harvard’s Osher Integrative Medicine Center to be excellent. His pragmatic approach of introducing research skills to his faculty and students, starting with the “publishable case report,” clinical research methods and seminar series, required courses on research, as well as electives, is highly innovative and progressive in helping CAM practitioners, faculty, and students become more oriented to the rules of evidence and the methods of scientific clinical inquiry. This NIH-funded research is doing much to help develop a culture of scholarship and academic rigor in his institutions and is helping to bridge the cultures of conventional and CAM researchers.

Another promising development is the rapid growth of the Consortium of Academic Health Centers for Integrative Medicine. The Consortium is composed of 39 North American academic health science centers that have active programs in at least 2 of the 3 areas of education, clinical care, and/or research in IM. This group started with 8 schools in 1999 and with the generous support of the Bravewell Philanthropic Collaborative has grown to its present size. The mission of the Consortium is as follows:

Our mission is to help transform medicine and healthcare through rigorous scientific studies, new models of clinical care, and innovative educational programs that integrate biomedicine, the complexity of human beings, the intrinsic nature of healing and the rich diversity of therapeutic systems.

With the voice of nearly 30% of US and Canadian medical schools, the Consortium is poised to advocate within academia for a relevant role for IM across all institutional missions. The
Consortium leadership consists of a steering committee member from each of the 39 schools. An executive committee is composed of chair (Victor Sierpina, University of Texas Medical Branch), vice chair (Adam Perlman, University of Medicine and Dentistry New Jersey), treasurer (John Pan, George Washington University), secretary (Anne Nedrow, Oregon Health Sciences University), and the past chair (Susan Folkman, University of California, San Francisco) and past vice chair (Mary Jo Kreitzer, University of Minnesota), as well as at-large members (Sara Warber, University of Michigan; Roberta Lee, Albert Einstein Medical School; Victoria Maizes, University of Arizona; David Rakel, University of Wisconsin; Bud Rickhi, University of Calgary; Saki Santorelli, University of Massachusetts Medical School).

The Consortium has operationalized its mission through its working groups. The Education Working Group, headed by Mary Guerrera from the University of Connecticut and Ron Glick from the University of Pittsburgh is actively involved in several projects, including proposing a change in educational standards to the Licensing Commission for Medical Education (LCME). The proposed changes are modifications of existing standards to include requirements for complementary and integrative medicine content into medical school curricula as well as an exposure to indigenous systems of care. If approved through the LCME's established process of revising standards, these changes will promote the field of CAM/IM concepts and content into the educational programs of all US medical schools. Each school would need to demonstrate that it teaches this material in some way and evaluates the results of such teaching in order to be accredited by the LCME. The Education Working Group is also compiling a database of educational resources in CAM/IM education available in the United States and Canada for other centers wishing to access such materials for their own ongoing or nascent programs.

Another initiative of this energetic working group is to create presentations about the need, rationale, and resources needed for fostering IM education, which will be presented to educational deans and other educators at the regional General Education Association meetings held as part of the Association of American Medical Colleges annual sessions this spring. Four proposals have been submitted for these regional meetings. The Education Working Group also submitted and had published a letter to the editor of the *Journal of Family Practice* arguing for incorporating integrative medicine into the design of residency programs. The group is also preparing a viewpoint paper on the changes needed in undergraduate, premedical curriculum in order to introduce premed students to the broad range of perspectives and skills needed to understand and practice integratively.

Several member schools (University of Arizona, University of Connecticut, Albert Einstein Medical School, University of Texas Medical Branch), led by University of Arizona Program in Integrative Medicine’s Patricia Lebensohn and Victoria Maizes, are developing an Integrative Medicine in Residency curriculum. This pilot started with a 12.5-hour online botanical curriculum and will be launched in July 2008 at 8 pilot family medicine residencies (4 Consortium members) as a 250-hour longitudinal, required curriculum across the 3 years of training. A student leadership committee is being formed to help foster leadership training at the American Medical Student Association.

The Clinical Working Group, led by Andy Heyman, an Integrative Fellow from the University of Michigan, and Jillian Capodice, Columbia University, has a number of activities in progress initiated by the previous co-chairs, Mary Hardy from UCLA and John Pan from George Washington University. Eight schools have institutional review board approval, and 4 more are pending to participate in The Outcomes Research Project to examine patient outcomes related to IM. Enrollment is underway. A new initiative involves joint conference calls with the Society for Integrative Oncology. A pediatric subgroup is also active with monthly conference calls and a number of initiatives in their specialty area. The Clinical Working Group also has developed a Clinical Models Survey, which is an audit of clinical services of Consortium members. This group also is developing the infrastructure for a practice-based research network in collaboration with the Research Working Group.

The Research Working Group, led by Susan Gould Fogerite, University of Medicine and Dentistry of New Jersey, and Laurie Lachance, University of Michigan, is in the process of creating a network of researchers from the various schools to share their expertise and patient populations for recruitment in studies in IM. By developing a membership database with information about research, practice, areas of expertise, and ongoing projects, they anticipate fostering collaboration and mentoring among members. This information also will be used to establish a Rapid Response and Referral Network for responding to questions from the media and providing comment on topics related to CAM and IM. The Research Working Group will be an instrumental part of a number of Consortium and non-Consortium peer reviewers of abstracts submitted for the North American Complementary and Integrative Medicine Research Conference to be held in Minneapolis in May 2009. This conference offers opportunities for researchers from the worldwide CAM community to present their best work on education, clinical, and other research areas in IM. The last conference, held in Edmonton, Alberta, Canada, in May 2006 was an enormous success, with over 700 attendees from 14 countries and hundreds of posters, presentations, theme sessions, and keynotes. We will soon be inviting proposals and encourage you to submit your best work. *ATHM* published the last conference proceedings.

Another vital activity of the Consortium is the policy domain, where our stated goal is to “inform national policy that advances integrative medicine through research, clinical, and education initiatives.” Mary Jo Kreitzer of the University of Minnesota is the liaison to the Executive Committee on policy matters. An attractive, informative “leave behind” describing the Consortium was developed and is being used to initiate dialogues with legislators, policy makers, and other opinion leaders. We are in the process of developing a process and policies for establishing alliances for collaboration and networking with other...
organizations in the CAM community, such as the Academic Consortium for Complementary and Alternative Health Care (ACCAHC) and others, with arranging bi-annual meetings with NCCAM leadership and developing relationships with campus Government Relations Officers in member schools.

The Consortium is preparing to expand its membership as more activity is clearly evident at other academic centers. We are also seeking to expand our revenue streams from membership dues and new sources of philanthropy and to explore potential business and intellectual property opportunities. For a complete list of member schools and other Consortium information, visit the website at www.imconsortium.org.

While the future of IM education is bright, some major challenges and opportunities lie ahead for us to prepare the next generation of integrative medicine practitioners. Among these are

1. Faculty development in both conventional and CAM schools regarding the content of the field, teaching methods, and research expertise;
2. Transprofessional collaboration in education, research, clinical care, and healthcare policy among IM practitioners and colleagues in conventional medicine, allied health, nursing, pharmacy, and CAM disciplines such as chiropractic, massage, naturopathy, indigenous healthcare systems, and others;
3. Providing learners with critical thinking skills, access to reliable resources, and role modeling of integrative practice in consistent, credible, and relevant ways;
4. Outcomes-based practice and optimal care pathways informed by research; and
5. Changes in health insurance reimbursement and policy to provide broader access for underserved patients to integrative medicine.

To forward such an agenda, the Consortium must partner with other CAM organizations and professional educators, deans, and course directors in our medical, nursing, and allied health schools; researchers; health policy and opinion-leaders; patient advocacy groups; and the scientific community. Together, we can change the world of healthcare.

REFERENCES
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EFFICACY OF LIFESTYLE CHANGES IN MODIFYING PRACTICAL MARKERS OF WELLNESS AND AGING

Steven Cameron Masley, MD, FAAFP, CNS; Wendy Weaver, BA; Gil Peri, MPH, MBA; Sharon E. Phillips, MSPH

Purpose • To determine the efficacy of asking people to add fiber, exercise, and stress management to their lifestyles to enhance markers of wellness and aging.

Methods • A 10-week, randomized control study conducted in a wellness center in St Petersburg, Florida. Participants were adults aged 21 to 65 years who exercised fewer than 3 days per week. Fifty-six subjects were randomized to a control or an intervention group. Subjects followed a diet with >30 g of fiber and <16 g of saturated fat daily and were taught to reach 70% to 85% of their maximum heart rate 5 to 6 days per week and to perform strength training 3 days per week. They were also asked to participate in 10 to 20 minutes of stress management activities daily. The study was designed to determine changes in body composition, maximal rate of oxygen consumption (VO2 max), total cholesterol: high-density lipoprotein (TCHDL) ratio, and cognition.

Results • Initial analyses with analysis of variance (ANOVA) comparing the intervention group to the control group showed significant improvements in TCHDL (8.9% average; P=.02) and change in weight (2.3 kg average; P=.016). When the groups were compared, the improvements in cognitive flexibility and VO2 max with ANOVA were not significant (P=.17 and P=.11, respectively).

Additional independent t tests showed decreases in TCHDL of 8.9% (P=.02) and TC of 7.3% (P=.001) for the intervention group compared to the control group. A mean increase of 29% in VO2 max of intervention subjects who exercised aerobically for at least 30 minutes 5 days/week was significant (P=.02) compared to the control group. Over the 10 weeks, the control group showed no significant change in lipids, body composition, cognition, and fitness, whereas the intervention group showed decreased body mass index (BMI) of 0.72 (P=.02), weight loss of 2.3 kg (P=.016), and decreased body fat of 1.6% (P=<.0001). In the intervention group, those with a BMI >24 who exercised 5 to 6 days/week lost 4.8 kg and 4.1 kg in body fat. Also, in the intervention group, several of the cognitive scores showed statistically significant improvements from baseline: mental speed (4.6%, P=.004), reaction time (4.5%, P=.023), and cognitive flexibility (11.7%, P=.019), but none of these cognitive changes was significant with independent t testing when compared to the control group.

Conclusions • A diet high in fiber and low in saturated fat combined with strength training, aerobic activity, and stress management activities improves fitness and several markers of wellness and aging. (Altern Ther Health Med. 2008;14(2):24-29.)

Steven Masley, MD, FAAFP, CNS, is president of the Masley Optimal Health Center and a clinical assistant professor in the Department of Family Medicine at the University of South Florida, both in St Petersburg. Wendy Weaver, BA, was the fitness coordinator at and Gil Peri, MPH, MBA, was director of the Carillon Wellness Center at St Anthony’s Health Care, St Petersburg, when this article was written. Sharon E. Phillips, MSPH, is a biostatistician III in the Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee.

Increasing obesity, epidemic rates of type 2 diabetes and the metabolic syndrome, low-nutrient diets, and lack of activity play key roles in the decline in fitness, health, and potential longevity in average Americans.1,3 Evidence-based lifestyle interventions are indicated to offset this potential decrease in lifespan and health span. Many diet studies have assessed weight loss and lipid response, yet few have combined dietary changes specifically addressing fiber and saturated fat intake with aerobic exercise and strength training and measured their impact on various measures of wellness, in particular, body composition (lean and fat mass), total cholesterol:high-density lipoprotein (TCHDL) ratios, strength, flexibility, maximal rate of oxygen consumption (VO2 max), and cognitive performance.

After age 40, steady physiological changes in age occur yearly, with body fat increasing by 1% and body lean mass decreasing by 1%. These changes are associated with losses in strength and an increased risk for both morbidity and mortality.4,12 Aerobic fitness also drops linearly, best noted by a VO2 max decrease of 1% per year after age 40.11-12 Every decade these measures worsen by approximately 10% with normal aging; hence, they appear to be useful measures of wellness.

Total cholesterol levels have been suggested to increase linearly through adulthood until age 70, by approximately 1 mg/dL yearly, with HDL levels changing minimally over this time frame.15 Studies have shown that low-density lipoprotein (LDL) receptor activity decreases with advancing age and appears to be
associated with an increase in LDL and TC levels without impacting HDL levels. As the TC:HDL ratio is easy to measure and has been shown to be one of the best predictors for developing cardiovascular disease (CVD), this makes the TC:HDL a practical predictor of CVD and potentially a useful marker of health.

Lastly, cognitive function as measured by reaction time, mental speed, and cognitive flexibility also has been suggested to decrease linearly over time. Enhancing cognitive function would likely also be important in improving overall productivity. Hence, various outcome markers exist that are potential physiological measures of wellness and can be used to assess the efficacy of various lifestyle interventions.

Our hypothesis was that combining aerobic activity and strength training with a diet emphasizing high fiber and low saturated fat intake plus a stress-management component could improve cholesterol profiles, body composition, strength, aerobic fitness, flexibility, and cognitive performance.

METHODS

St Anthony’s Hospital’s institutional review board approved this protocol, and all subjects gave written informed consent to participate. Subjects 21 to 65 years of age, enrolled in a wellness center in St Petersburg, Florida, and exercising fewer than 3 days per week were invited to participate. Our aim in enrolling wellness center members who were not using the facilities regularly was to find subjects willing to participate in a study assessing markers of fitness and wellness with a diet and exercise regimen; these subjects would be similar to average Americans in terms of body mass index (BMI), dietary intake, and fitness. At entry the subject’s average BMI was 28.9, daily fiber intake was 22 g of saturated fat, and VO2 max was 41.3, compared to national American averages of 26.6 BMI, fiber intake of 15.6 g, saturated fat intake of 27.9 g, and VO2 max of 38.5.

Fifty-six subjects were ranked by BMI to help ensure similar BMI and fitness levels at entry and randomized to either a control or an intervention group for 10 weeks. At entry there was no statistical difference in BMI; gender distribution; age distribution; body fat percentage; VO2 max; or TC:HDL ratios, TC, or HDL levels between the control and intervention groups (Table 1).

Members of the control group were asked to continue their current dietary intake and activity level for 10 weeks, and in addition to the listed outcome measures, their dietary intake was assessed with NutriBase 5 software (CyberSoft Inc, Phoenix, Arizona) at entry and end of the study. After the study was completed, control subjects were invited to participate in the intervention.

The intervention program participants were taught by a nutritionist and American College of Sports Medicine (ACSM)-certified exercise instructors during weekly lectures in a group setting using meal plans and recipes for a diet with >30 g of fiber and <16 g of saturated fat daily. They were encouraged to reach 70% to 85% of their maximum achieved heart rate 5 to 6 days per week for 30 minutes and to perform strength training 3 days per week with 1 to 2 sets of 10 to 15 repetitions for 10 body movements to smooth-motion lifting exhaustion for a total of 10 weeks. The emphasis upon adding fiber and decreasing saturated fat has been described previously. In addition, intervention subjects were encouraged to create 10 to 20 minutes each day for mentally calming activities, such as meditation, breathing activities taught in a yoga class, or enjoying a hot bath by candlelight with soft music.

Outcome measures included body composition, strength and flexibility, VO2 max, TC:HDL ratios, and cognitive function. Body composition was measured with bioelectrical impedance (Tanita® TBF-310, Tanita Corp of America, Inc, Arlington Heights, Illinois). Strength and flexibility data were collected using instructions from the ACSM for curl-ups (abdominal crunches), push-ups, and sit-and-reach flexibility. VO2 max was predicted from peak MET (exercise measure of metabolic equivalent) and heart-rate levels achieved during a treadmill test using the Bruce protocol—a standardized multistage treadmill test for assessing cardiovascular health—with Physiologic® software (KI Software, Silver Spring, Maryland). TC and HDL were measured with Cholestech® (Cholestech Corp, Hayward, California) using reflectance photometry to measure the amount of cholesterol fractions in the blood, which is converted to a mg/dL measurement. At entry and following the 10-week intervention, neurocognitive performance was assessed using a computerized battery, CNS Vital Signs® (CNS Vital Signs, LLC, Chapel Hill, North Carolina). This test battery is self-administered in 30 minutes on a PC and includes tests of visual and verbal memory, finger tapping, symbol digit coding, the Stroop test, shifting attention, and continuous performance. The 7 tests generate domain scores for memory, psychomotor speed, information processing time, attention, and cognitive flexibility. The tests in the CNS Vital Signs battery are standardized and are known to be valid, reliable, and sensitive to

### Table 1: Demographic Data of Subjects at Entry

<table>
<thead>
<tr>
<th>Measures</th>
<th>Control Group (N=28)</th>
<th>Intervention Group (N=28)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>39.3%</td>
<td>53.6%</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>43.5 (11.2)</td>
<td>47.1 (9.4)</td>
<td>—</td>
</tr>
<tr>
<td>Years of education</td>
<td>16.3</td>
<td>15.8</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI</td>
<td>28.6 (6.6)</td>
<td>29.3 (6.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Body fat percentage</td>
<td>30.8% (8.8)</td>
<td>33.0% (9.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>4.2 (1.5)</td>
<td>4.5 (1.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>VO2 max</td>
<td>41.4 (12.0)</td>
<td>41.2 (9.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mental speed</td>
<td>171.1 (23.9)</td>
<td>175.9 (25.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>Reaction time</td>
<td>692.4 (85.6)</td>
<td>667.3 (101.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Attention</td>
<td>8.2 (5.1)</td>
<td>11.2 (19.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>43.3 (9.5)</td>
<td>44.4 (14.8)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; TC:HDL, total cholesterol: high-density lipoprotein; VO2 max, maximal rate of oxygen consumption.*
very small changes in neurocognitive performance.\textsuperscript{1,5}

Dietary adherence was measured using NutriBase 5® software, analyzing 3-day food intake records with 2 weekdays and 1 weekend day at entry and after 10 weeks to assess dietary changes. Subjects were asked to calculate their fiber and saturated fat intake 1 day per week using provided tables. Activity levels and stress-management activities were reported verbally weekly with an exercise physiologist who recorded frequency and intensity of strength training and aerobic activity and whether subjects participated in calming activities for 10 to 20 minutes daily over each week.

Power calculations were performed to determine the sample size, such that an independent \( t \) test would be based on a power of 0.85 to detect a significant difference (\( P = 0.05 \), 2-sided) based on projected changes in the measures for BMI, the TC:HDL ratio, and percentage of body fat from previous pilot studies, resulting in a requirement of 23 patients per group. After allowing for a 20% dropout rate, we planned to enroll 28 patients per group. We did not have data to assess sample size for changes in strength, cognitive performance, or VO\(_2\) max; hence, the primary outcome measures would be changes in TC:HDL, BMI, and body fat. Secondary measures would be changes in strength, VO\(_2\) max, and cognitive performance. ANOVA was used to compare the intervention group with the control group for changes in TC:HDL, weight, cognitive flexibility, and VO\(_2\) max.

Between-group and within-group differences were tested using independent and paired \( t \) tests. Weight change was analyzed for both groups and for overweight subjects (BMI >24, which is the cut-off for normal weight) in each group. Likewise, TC:HDL changes were measured in both groups and for subjects who started with a TC:HDL >4.8, which is considered abnormal by some national commercial laboratories. Diet and exercise compliance was assessed using the weekly data collected by the exercise physiologists and analyzed. Of the initial 28 intervention subjects, 1 dropped out at the beginning because of a family emergency, and the remaining 27 completed the study. Of the 28 control subjects, 2 dropped out immediately for personal reasons, and 6 were unwilling to complete testing at the end of 10 weeks. Hence, 27 of 28 intervention and 20 of 28 control subjects completed the study.

**RESULTS**

Over the 10 weeks, the control group showed no significant change in BMI, total weight, body fat percentage, TC:HDL ratio, VO\(_2\) max, or cognitive performance as assessed by mental speed, reaction time, and cognitive flexibility. ANOVA comparing the intervention group to the control group showed significant changes in weight loss, an average of 2.3 kg (\( P = 0.016 \), standard error 1.7), an average 8.9% improvement in the TC:HDL ratio (\( P = 0.02 \), standard error 1.1), and non-significant changes in cognitive flexibility (\( P = 0.17 \), standard error 12.1) and VO\(_2\) max (\( P = 0.11 \), standard error 9.5).

Compared to the control group over 10 weeks with an independent test, the intervention group showed a significant decrease in BMI (0.72, \( P = 0.02 \)), weight (2.3 kg, \( P = 0.016 \)), and percentage of body fat (1.6%, \( P = 0.001 \)), without a loss in lean mass with an independent \( t \) test. The 16 control subjects with a BMI >24 at entry noted a 0.2-kg decrease in weight (\( P = 0.7 \)); however, their body fat increased 0.6%. In contrast, the 20 intervention subjects with a BMI >24 noted a 2.3-kg weight loss (\( P = 0.001 \)) with a 1.7% decrease in body fat. Finally, the 7 in the intervention group with a BMI >24 and who exercised at least 5 to 6 days per week lost 4.3 kg in body weight and 4.1 kg in body fat (\( P = 0.009 \)), which represents a 2.6% decrease in body fat and a 12.8% loss in their total fat mass (Figure 1).

The intervention group also showed an 8.9% decrease in TC:HDL (\( P = 0.02 \)) and a 7.3% decrease in TC (\( P = 0.001 \)). Although not statistically significant, in subjects who had abnormally elevated TC:HDL levels at entry (>4.8), there was an 11.7% (5.97 to 6.73) increase in the 7 control subjects and a 12.7% (6.26 to 5.46) decrease in 10 intervention subjects (Figure 2).

![FIGURE 1 Changes in Weight and Fat Mass Over 10 Weeks as Measured With Bioelectrical Impedance](image1)

![FIGURE 2 Changes in the TC:HDL Ratio Over 10 Weeks](image2)
With a paired t-test and following ACSM methods, the intervention group noted a 91% increase in the number of curl-ups they could do, (44.7 to 85.7, P<.0001); a 79% increase in the number of push-ups they could do (10.1 to 18.1, P<.0001); and a 30% increase in sit-and-reach flexibility (20.1 cm to 26.2 cm, P=.0008) over the 10 weeks (Figure 3). Strength and flexibility testing was used as part of the intervention and not tested in the control group.

The mean increase of 17% in VO2 max in the intervention group was not different (P=.11) from the control group. After comparing only intervention subjects who exercised aerobically for at least 30 minutes 5 to 6 days per week (n=13), the mean 29% increase in VO2 max in the intervention subjects was significant (P=.02) compared to the control group (Figure 4). In the intervention group, increasing fiber intake to >30 g daily compared to an intake of <30 g also was associated with an increase in VO2 max (P<.0001).

This study did not show a statistically significant difference in cognitive function by independent t testing when comparing the intervention and control groups. For within-group comparisons, there were no statistically significant changes in the control group from baseline to follow-up. Of interest within the intervention group is that several of the cognitive scores showed statistically significant improvements from baseline: mental speed (4.6%, P=.014), reaction time (4.5%, P=.023), and cognitive flexibility (11.7%, P=.019). The intervention groups’ changes in attention were not significant (45%, P=.18, Table 2). Hence, there is a non-significant trend for cognitive improvement for mental speed, reaction time, and cognitive flexibility in the intervention group, and further studies with larger samples sizes are warranted.

In the intervention group, 70% of the subjects reached at least 30 g of fiber daily, 78% decreased their saturated fat intake to <16 g daily, 48% exercised in their aerobic heart rate range at least 5 to 6 days per week, and 56% engaged in strength training at least 3 days per week. As evidenced by the average nutritional intake with the NutriBase 5 software, no significant changes occurred in the control group. The intervention group reported a calorie intake decrease from 1898 kcal to 1511, a fiber intake increase from 15 to 28 g daily, and a saturated fat intake decrease from 22 to 11 g daily.

In comparing whether adherence to the various aspects of the program (dietary change, activity change, or stress management) achieved significant reduction in these objective measures of wellness and aging, we compared the results of the intervention group who adhered to each intervention against those who did not with paired t tests. Participating in exercise 5 to 6 days per week appeared the most important, followed by increasing fiber intake, adding strength training, and reducing saturated fat intake. Adding stress management activities (as defined by creating peaceful time daily) did not impact the final outcome measures.

**DISCUSSION**

This intervention combined dietary changes, activity recommendations, and stress management and then gauged basic outcome measures that reflect fitness and markers for wellness and aging. Five areas were assessed, including changes in body fat, strength, aerobic fitness, cholesterol, and cognitive performance. Significant improvements were seen in the first 4 of these areas, and a trend toward improvement was seen in 3 of the 5 domains of cognitive function that were assessed in this study.

The weight loss noted in this study as a result of adding the recommended extra 250 kcal in exercise daily (350 calories x 5 days per week) and decreasing caloric intake by 350 calories would have been expected to decrease body weight by 5.4 kg. This is close to the 4.8-kg weight loss noted in the study in those who were adherent and overweight. Overall, the focus on adding at least 30 g of fiber daily gained wide adherence and may have added to the success of this intervention.
The general public can easily perform most of the outcome measures chosen for this study. Strength tests used in this intervention with charts from the ACSM provide comparisons of results to gender- and age-specific groups. The TC:HDL ratio is perhaps the best predictor of risk for cardiovascular disease and can be measured easily in a non-fasting state at health fairs, clinics, and fitness centers across the country, often for free or for a nominal fee. The improvement noted in TC:HDL is similar to that in previous studies.21 Fitness centers and medical professionals across the country provide body composition testing with skin-fold testing, and electrical impedance testing is becoming increasingly common. Aerobic fitness testing can be performed in a medical facility when warranted and also can be assessed in almost any fitness center that has treadmill machines. Of these tests, only cognitive test- ing is not yet practical on a large scale without medical referral and is not yet validated for use in the general public. Most wellness centers, and as no significant changes occurred in the control group, the study results do not appear to have been biased.

We acknowledge that it would have been preferable to measure VO₂ max directly rather than estimating it and to assess detailed lipid profiles and other more advanced measures of cardiovascular disease risk, including C-reactive protein levels; however, these additional outcome measures were beyond the scope of this initial study. We noted an apparent improvement in VO₂ max in subjects who increased their fiber intake, but this study was not designed or powered to distinguish between benefits from exercise and benefits from nutritional intake. Although it is plausible that more optimal nutritional intake could improve VO₂ max independent of exercise, further studies are warranted to assess this finding.

Bioelectrical impedance testing has true limits in measuring

### TABLE 2 Changes in Cognitive Function*

<table>
<thead>
<tr>
<th>Mental Speed</th>
<th>Reaction Time†</th>
<th>Attention†</th>
<th>Cognitive Flexibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group at entry</td>
<td>171</td>
<td>692</td>
<td>8</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(23.9)</td>
<td>(85.6)</td>
<td>(5.1)</td>
</tr>
<tr>
<td>Control group post-10 wks</td>
<td>176</td>
<td>666</td>
<td>8</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(20.0)</td>
<td>(90.7)</td>
<td>(4.7)</td>
</tr>
<tr>
<td>(% improvement)</td>
<td>(3%)</td>
<td>(3.7%)</td>
<td>(0%)</td>
</tr>
<tr>
<td>Intervention group at entry</td>
<td>176</td>
<td>667</td>
<td>11</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(25.2)</td>
<td>(101.4)</td>
<td>(19.5)</td>
</tr>
<tr>
<td>Intervention post-10 wks</td>
<td>183</td>
<td>637</td>
<td>6</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(25.0)</td>
<td>(97.9)</td>
<td>(3.5)</td>
</tr>
<tr>
<td>(% improvement)</td>
<td>(4.6%)</td>
<td>(4.5%)</td>
<td>(45%)</td>
</tr>
<tr>
<td>Intervention group at entry, activity 5+ d/wk</td>
<td>175</td>
<td>681</td>
<td>9.7</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(29.5)</td>
<td>(99.7)</td>
<td>(10.0)</td>
</tr>
<tr>
<td>Intervention group post-10 wks, activity 5+ d/wk</td>
<td>184</td>
<td>619</td>
<td>5.4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>(27.5)</td>
<td>(55.5)</td>
<td>(2.9)</td>
</tr>
<tr>
<td>(% improvement)</td>
<td>(5.1%)</td>
<td>(9.1%)</td>
<td>(44.3%)</td>
</tr>
</tbody>
</table>

*Changes were measured using CNS Vital Signs testing.
†A decrease in reaction time score and attention score indicates improvement.
lean mass as it varies with hydration. Measures were taken to standardize hydration, caffeine, exercise, alcohol, and time-of-day factors that influence hydration and body composition measures.

The dropout rate in the control group did limit the analyses in this study but fell within the allowable overall rate for our sample size calculations. However, many members of the control group who declined to complete their final evaluation noted that their status had worsened from the starting time in late September to completion in mid-December and that they did not want to document their deterioration. Therefore, their inclusion likely would have enhanced the outcome for the intervention group rather than detracted from the results.

CONCLUSION

A 10-week lifestyle program with a diet emphasizing high fiber intake (>30 g daily) and <16 g of saturated fat daily (which are consistent with USDA recommendations) combined with strength training 2 to 3 times per week, aerobic activity 5 to 6 days per week, and stress management improves multiple measures of wellness and aging. These enhancements, compared to a randomized control group, include TCHDL ratios, VO2 max, performance, body fat mass, strength gains, and flexibility gains. This intervention program can also be associated with gains in cognitive performance.

Although this combination of recommendations requires further study, an approach that focuses on implementing a combination of fiber, aerobic activity, strength training, and stress management achieves multiple improvements in wellness and aging.

Acknowledgments

This study was funded by St Anthony’s Health Care and conducted at the Carillon Wellness Center in St Petersburg, Florida.

REFERENCES


 Which One Is The Culprit?

If Delayed Food Allergies Are To Blame, The ImuPro300 Allergy Test Can Help.

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Abstract
The present study was undertaken to compare the bioavailability of calcium after supplementation with four preparations - Calcium AA Chelate (18%; A), Dicalcium malate (B), Calcium AA Chelate (26%; C) and Calcium carbonate (D). A single dose containing 900 mg of elemental calcium, no significant differences were observed in AUC suggesting that bioavailability of all four Supplements is similar. However, there were significant differences between the groups in the maximum concentration (Cmax), time to reach maximum concentration (Tmax) and half-life of elimination. Supplement A showed the maximum increase in serum calcium concentration compared to baseline followed by Supplements B, C and D. Time required to reach the maximum serum concentration was shortest for Supplement D followed by Supplements C, A and B. This suggests that absorption of Supplement D is better compared to the other Supplements. However, the half-life of Supplement D in serum was shortest suggesting that it is cleared from the body faster than the other Supplements. Supplement B had the longest half-life and seems to be most bioavailable followed by supplement A, C and D. This work was sponsored by Albion Advanced Nutrition.

Introduction
According to the Osteoporosis Society of Canada, approximately 1.4 million Canadians suffer from osteoporosis (www.osteoporosis.ca). Although more prevalent in older women, older men and younger individuals also get the disease. The cost of treating osteoporosis and the fractures it causes is estimated to be $1.3 billion each year in Canada. Given the increasing proportion of older people in the population over the next few years, these costs, as well as the number of individuals with osteoporosis, will likely rise. Adequate calcium intake is necessary for bone remodeling to take place in healthy individuals. In older adults adequate calcium intake can slow bone loss and lower the risk of fracture (Lin and Lane, 2004). Furthermore, calcium supplementation is an important part of the medical management of osteoporosis in combination with various prescription medications.

Calcium bioavailability is important when calcium intakes are low, or when an individual is growing or losing bone (Fairweather-Tait and Teucher, 2002). Calcium absorption is dependent on many dietary and environmental factors, including the level of protein, sodium, caffeine, vitamin D, fructose and phosphorous in the body. Furthermore, one’s genetic makeup, including the vitamin D receptor genotype, may also play a role in calcium absorption (Dawson-Hughes et al., 1995). Supplementation with various calcium preparations is now the most common approach to increase calcium intake in individuals concerned with osteoporosis. However, it has been shown that the bioavailabilities of many commercial calcium preparations are different (Fairweather-Tait and Teucher, 2002). The most common calcium supplement, calcium carbonate, is known to be generally well absorbed but other calcium forms, such as citrate, malate and amino acid chelate, have shown superior efficacy in some studies (Sakhaee et al., 1999, Heaney et al., 1990).

Objective
The objective of this study was to compare in healthy individuals the bioavailability of calcium from four separate calcium-containing products. This information will increase the overall knowledge of these compounds.

Methods
The calcium treatments are identified in the following table:

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Supplements</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium amino acid chelate (18%)</td>
<td>A</td>
<td>15</td>
</tr>
<tr>
<td>Dicalcium malate</td>
<td>B</td>
<td>15</td>
</tr>
<tr>
<td>Calcium amino acid chelate (26%)</td>
<td>C</td>
<td>15</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>D</td>
<td>15</td>
</tr>
</tbody>
</table>

Study Outline
Individuals were studied for a total of approximately 5 weeks. All subjects were studied as outpatients. The screening process consisted of CBC count, platelets, electrolytes, glucose, BUN, creatinine, liver function tests, total protein, albumin, calcium, phosphorous, PT/PTT, and urinalysis. Women of childbearing age also had a urine pregnancy test. Subjects were asked questions to determine present health and past medical history and underwent a brief physical exam. Those deemed eligible after the screening process were asked to return for the four supplementation days. On the first supplementation day, subjects were randomized for receiving the four Supplements in a random order. Blood was taken immediately before supplement administration and 0.5, 2, 4, 6, 9 and 12 hours after the dose. Standard low calcium meals, breakfast, lunch and dinner, were provided immediately after the dose, following the 4-h blood sample and following the 9-h blood sample, respectively. Each individual was given 6 capsules containing a total of 900 mg of elemental calcium. This dose of elemental calcium is within the RDI recommended by the United States National Institutes of Health (United States National Institutes of Health 1994. Optimal calcium intake. NIH Consensus Statement, Vol. 12, No. 4. 31 pp.) Each subject returned three more times for supplementation with the identical level of elemental calcium in an alternative form. Each visit was separated by a minimum of 1 week. The identical food was supplied to the subjects on each supplementation day. Blood levels of calcium were determined at each time point.

Blood: Peripheral blood was taken by venipuncture prior to baseline to determine baseline levels from baseline. A significant difference was observed in the Supplement D-treated group.

The study design is summarized in the following figure:

![Figure 1](image)

The participants, clinical assistants and those assessing the outcome were blinded to the group assignment.

Results
The data presented in the following table show the changes between the groups in serum calcium concentrations at all the time points after oral supplementation.

<table>
<thead>
<tr>
<th>Serum Calcium Concentration (mg/dl)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Supplement A</td>
<td>2.34</td>
</tr>
<tr>
<td>Supplement B</td>
<td>2.38</td>
</tr>
<tr>
<td>Supplement C</td>
<td>2.40</td>
</tr>
<tr>
<td>Supplement D</td>
<td>2.44</td>
</tr>
</tbody>
</table>

Symbols (*, #, $ and +) represent corresponding groups with statistically significant differences (p<0.05).

It was observed that supplementation with A, B and C elevated the serum calcium levels from baseline. A significant difference from baseline within the Supplement A, B and C-treated groups was observed for all time points except for 0.5 hours. Also in the Supplement B-treated group at 2 hours there was no significant difference from baseline. No Significant difference was observed in the Supplement D-treated group.
From Various Calcium-Containing Products
A Bioavailability Study

Pratibha Chaturvedi1, Rinee Mukherjee1, Meagan McCorquodale1, Dave Crowley1, Stephen Ashmead2 and Najla Guthrie1KGK Synergize Inc., 2Albion Human Nutrition

Discussion

In the present study, the pharmacokinetic characteristics and bioavailability of four calcium components were investigated. It was observed that all the supplements had a poor bioavailability as suggested by the low values for AUC. This could be due to the elimination of the majority of the supplement after the first pass through the liver.

The results demonstrated that an oral administration of Supplement B (900 mg dose) led to more bioavailable calcium compared to the other three supplements.

Remarkably little is known about the relative efficacy of amino acid chelates of calcium. In the only commonly cited trial, absorption was measured for an amino acid chelate called calcium bisglycinate and compared with absorption from citrate, carbonate, and MCHC (Heaney, et al., 1990). In that trial, the amino acid chelate showed the best absorption and MCHC the worst. Although CCM was studied in that trial, it was taken under different circumstances than the chelate (with meals), so drawing definitive conclusions is not possible.

In this study, Dicalcium malate was found to be more bioavailable than the amino acid chelate form of calcium with almost similar absorption but with Dicalcium malate having a longer half-life.

Conclusion

The present study was undertaken to compare the bioavailability of calcium after supplementation with four preparations. It was observed that the calcium present in the four Supplements is absorbed and is bioavailable in humans and can be detected in serum after ingestion of a single dose containing 900 mg of elemental calcium.

All the Supplements had a poor bioavailability as suggested by the low values for AUC. This is likely due to substantial first-pass elimination. Based on the results of this study, Supplement B seems to be the most bioavailable than other Supplements with a longer half-life followed by Supplement A, C and D.

References


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Low back pain poses a major economic burden to society and to employers. Back pain is common, and in general, prognosis is good, with 60% to 70% of patients recovering within 6 weeks. However, the largest percentage of the costs of back pain, including the more than $28 billion (1998 USD) in productivity losses (which inflated to 2007 USD is more than $36 billion), is concentrated in the small percentage of patients with chronic low back pain.

Conventional treatments for chronic low back pain have been found to be expensive and ineffective. Consequently, a significant number of patients have turned to complementary and alternative medicine (CAM). One survey of patients eligible for insurance coverage for CAM found that 55% of low back pain patients had at least 1 visit to a CAM provider in the study year, and 43% used only CAM for their back pain.

Naturopathic care also significantly reduced societal costs by $1212 per participant. From the perspective of the employer, the intervention cost $154 per absentee day avoided (compared to employer costs of lost productivity of $172 per day) and had a return on investment of 7.9% under the healthcare coverage limits set by this employer and assuming the employer paid the full cost of naturopathic care. Participants experienced savings in adjunctive care of $1096 per participant.

This study is an economic evaluation carried out alongside a pragmatic randomized control trial showing the cost-effectiveness of naturopathic care compared to a standardized physiotherapy education regimen in the treatment of chronic low back pain. Further studies of the economic impact of naturopathic medicine are warranted.

METHODS
In the trial, workers aged 18 to 65 years with a clinical diagnosis of low back pain of at least 6 weeks’ duration and who were not on sick leave were recruited from a warehouse site of a large North American corporation. After informed consent, 75 who were eligible (Figure 1) were randomly assigned (via observed coin toss) to receive 3 months of 30-minute semi-weekly onsite naturopathic care visits (acupuncture, exercise and dietary advice, relaxation training, and a back care educational booklet) or 3 months of 30-minute bi-weekly onsite control group visits (standardized physiotherapy advice and the back care educational booklet).
Study participants in both groups were told to continue their usual pain medications as needed, and this usage was monitored. Participants’ use of other adjunctive care (chiropractic care, massage, and physiotherapy) was also monitored but not guided in any way by the study. The study was approved by the McMaster University Research Ethics Board, and more detail on the study design is available in Szczurko et al.11

The cost-effectiveness of naturopathic care over the control intervention is calculated for 3 perspectives: societal, employer, and participant. Because the cost-effectiveness of this intervention to the employer and to participants depends on coverage limits and the resulting allocation of healthcare costs (both of which can vary widely across employers), the main perspective for this study is societal. The effectiveness of the intervention in terms of the Roland-Morris Disability Questionnaire (RDQ), the Oswestry Disability Index (ODI), and a visual analog scale for pain has been established.11 Here effectiveness for the societal and participants’ perspectives is measured in terms of quality-adjusted life-years (QALYs) gained over 6 months (3-month treatment period plus 3-month follow-up). The algorithm devised by Brazier et al.,12 a single index measure of health-related quality of life (HRQoL)—the SF-6D—is used to calculate QALYs for each participant at baseline, 1 month, 2 months, 3 months, and 6 months from responses to the SF-36 at each of these time points. Total change in QALYs is calculated as the area under the SF-6D score curve over the 6-month study period. Cost-effectiveness to the employer is calculated in terms of cost per day of absenteeism reduced and return on investment. Given the short time horizon, neither costs nor effects are discounted.

Absenteism was not directly measured in this study. However, because productivity losses are such a large portion of the cost of low back pain,17 changes in absenteeism are estimated using the change in the RDQ. A search of the literature revealed several recent randomized controlled trials of various interventions for low back pain that measured both days lost from work and the RDQ. A study by Moffett et al.13 proved the best match in terms of average baseline RDQ levels (6.65 for the treatment group and 5.56 for controls), the intervention tested (exercise classes added to routine general practitioner care), and sample size (N=183). This study also provided the most conservative estimate of absentee days reduced per 1-point reduction (improvement) in the RDQ of 2.32 days per 1-point reduction in the RDQ maintained over 1 year.

Costs are reported in 2005 US dollars. The patients themselves reported their use of back pain–related adjunctive care at baseline, 1 month, 2 months, 3 months, and 6 months via 1-week diaries.14 Unfortunately, the unit cost of each type of adjunctive care was not recorded, and published sources of these costs (other than medication costs) are sparse. Therefore, the unit costs and resource use are reported separately to enable decision makers facing different costs to adjust the study’s results. As shown in Table 1, the best available source for unit price data for naturopathic care, massage, and physiotherapy was the national association for each type of practice. Published sources were available to value chiropractic care,15 over-the-counter and prescription drugs, and productivity losses.16

Published guidelines for the treatment of low back pain generally consist of patient education and reassurance, discouragement

---

**FIGURE 1 Flowchart of Subjects Through the Randomized Controlled Trial**

Study participants in both groups were told to continue their usual pain medications as needed, and this usage was monitored. Participants’ use of other adjunctive care (chiropractic care, massage, and physiotherapy) was also monitored but not guided in any way by the study. The study was approved by the McMaster University Research Ethics Board, and more detail on the study design is available in Szczurko et al.11

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The cost-effectiveness of naturopathic care over the control intervention is calculated for 3 perspectives: societal, employer, and participant. Because the cost-effectiveness of this intervention to the employer and to participants depends on coverage limits and the resulting allocation of healthcare costs (both of which can vary widely across employers), the main perspective for this study is societal. The effectiveness of the intervention in terms of the Roland-Morris Disability Questionnaire (RDQ), the Oswestry Disability Index (ODI), and a visual analog scale for pain has been established.11 Here effectiveness for the societal and participants’ perspectives is measured in terms of quality-adjusted life-years (QALYs) gained over 6 months (3-month treatment period plus 3-month follow-up). The algorithm devised by Brazier et al.,12 a single index measure of health-related quality of life (HRQoL)—the SF-6D—is used to calculate QALYs for each participant at baseline, 1 month, 2 months, 3 months, and 6 months from responses to the SF-36 at each of these time points. Total change in QALYs is calculated as the area under the SF-6D score curve over the 6-month study period. Cost-effectiveness to the employer is calculated in terms of cost per day of absenteeism reduced and return on investment. Given the short time horizon, neither costs nor effects are discounted.

Absenteism was not directly measured in this study. However, because productivity losses are such a large portion of the cost of low back pain,17 changes in absenteeism are estimated using the change in the RDQ. A search of the literature revealed several recent randomized controlled trials of various interventions for low back pain that measured both days lost from work and the RDQ. A study by Moffett et al.13 proved the best match in terms of average baseline RDQ levels (6.65 for the treatment group and 5.56 for controls), the intervention tested (exercise classes added to routine general practitioner care), and sample size (N=183). This study also provided the most conservative estimate of absentee days reduced per 1-point reduction (improvement) in the RDQ of 2.32 days per 1-point reduction in the RDQ maintained over 1 year.

Costs are reported in 2005 US dollars. The patients themselves reported their use of back pain–related adjunctive care at baseline, 1 month, 2 months, 3 months, and 6 months via 1-week diaries.14 Unfortunately, the unit cost of each type of adjunctive care was not recorded, and published sources of these costs (other than medication costs) are sparse. Therefore, the unit costs and resource use are reported separately to enable decision makers facing different costs to adjust the study’s results. As shown in Table 1, the best available source for unit price data for naturopathic care, massage, and physiotherapy was the national association for each type of practice. Published sources were available to value chiropractic care,15 over-the-counter and prescription drugs, and productivity losses.16

Published guidelines for the treatment of low back pain generally consist of patient education and reassurance, discouragement
of bed rest and recommendations for a gradual increase in activity, referral for exercise therapy (especially for chronic low back pain), and pain medication. Participants on prescription medications were assumed to manage those with their regular conventional physician. Visits to conventional physicians for prescription management or for non–back pain-related conditions were not assumed to vary between groups and were not tracked. The study naturopathic physicians provided both the naturopathic and control group care. In the real world, low back pain patients would not likely seek out naturopathic physicians to obtain physiotherapy advice at the exclusion of other naturopathic care. Therefore, the time the control group spent with the naturopathic physicians is valued at the cost of a physiotherapy visit. To account for the protocol-related time spent by both groups (informed consent and data collection), only half of the 1-hour screening visit (where histories were taken and initial exams performed) will be counted and a total of 45 minutes (15 minutes per data collection cycle times 3 cycles) will be subtracted from practitioner time for each group.

This analysis follows an intent-to-treat principle for participants who received at least 1 treatment, and missing data are handled using carry-forward imputation. Because the distribution of cost data tends to be highly skewed, bias-corrected and accelerated bootstrap estimates are used to determine confidence intervals for mean differences in costs (1000 replications). The bootstrapped societal cost-QALY pairs are also graphically represented on a cost-effectiveness plane.

Uncertainty in an economic evaluation comes not just from sample variation, but also from the assumptions made that can affect generalizability. In order to test the robustness of study results, a univariate sensitivity analysis is conducted. The use of each resource is varied over its 95% confidence interval range (Table 2), and in the absence of better data, the unit price of each resource shown in Table 1 is varied from 50% to 150% its value. In discussions with practitioners, these ranges are possible, especially if they are allowed to also capture variation in the length and intensity of each visit. The absenteeism estimate has 3 sources of uncertainty: labor costs, RDQ scores, and the change in absentee days for each point change in RDQ. Labor costs will be varied the same way other unit costs are varied, and RDQ scores are varied over their 95% confidence interval. The change in absentee days for each point change in RDQ is varied from a low of 0 days per RDQ point (essentially setting absenteeism to 0) to the higher rate seen in Kovacs et al of 3.59 days per 1-point change in the RDQ. All calculations are made using Microsoft Excel 2003 SP1 (Microsoft Corporation, Redmond, Washington).

RESULTS

The 75 workers were randomized to naturopathic care (n=39) or to a standardized physiotherapy education regimen (control group care; n=36). Overall, 68 patients (91%) had usable data for the 12-week treatment period, and 32 (82%) of the naturopathic care group and 8 (22%) of the control group had week 26 follow-up data (Figure 1). The primary reason why the response rate for the control group at week 26 is so low is because both groups were offered the opportunity to receive crossover care for 4 weeks after the treatment period ended (between week 12 and week 16) as an incentive for retention during the treatment period. Thirteen of the control group participants elected to receive crossover naturopathic treatment and were no longer able to represent control group outcomes at follow-up. No participants in the naturopathic care group elected to receive crossover control group care.

Resource use for the study treatments (net of protocol-related hours), adjunctive care visits and medication, and estimated absenteeism days (all net of baseline) are reported in Table 2.

### TABLE 1 Unit Prices and Sources for Each Resource Valued

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit price (USD)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naturopathic visit (per hour)</td>
<td>$125.00</td>
<td>Based on a range of $100 to $150 per hour reported via e-mail by American Association of Naturopathic Physicians staff</td>
</tr>
<tr>
<td>Chiropractic visit (per visit)</td>
<td>$60.70</td>
<td>Overall average cost of a visit from Segall (2004)</td>
</tr>
<tr>
<td>Massage visit (per visit, assuming a 1-hour visit)</td>
<td>$55.00</td>
<td>Based on a range of $50 to $60 per hour reported via e-mail by American Medical Massage Association staff</td>
</tr>
<tr>
<td>Physiotherapy visit (per visit, assuming a 30-minute visit)</td>
<td>$61.20</td>
<td>Based on the Canadian Physiotherapy Association’s recommended fee for private practice of $37.50 CAD per 15 minutes translated to US dollars using an exchange rate of 1.2254 CAD per USD</td>
</tr>
<tr>
<td>Medication costs</td>
<td>Varies</td>
<td>Medi-Span Master Drug Database* and <a href="https://www.drugstore.com">drugstore.com</a>†</td>
</tr>
<tr>
<td>Lost productivity (per hour, assumes productivity value to employer equals employer outlay for that employee)</td>
<td>$21.44</td>
<td>Employer cost for employee compensation—production, transportation, and material moving from Bureau of Labor Statistics (2005)‡</td>
</tr>
</tbody>
</table>

*Costs according to Medi-Span Master Drug Database (MDDB) v2.5; accessed August 2006.
†Costs according to www.drugstore.com; accessed October 2006.
‡Costs according to [drugstore.com](https://www.drugstore.com); accessed October 2006.
**TABLE 2** Average Use of Resources Net of Baseline Use and Health-related Quality of Life (SF-6D)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Naturopathic care (n=39)</th>
<th>Control (n=31)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study treatment 30-minute visits (net of protocol-specific hours)</td>
<td>23.5</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Adjunctive care over 6 months Mean (Bootstrap BCa 95% CI)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractic visits</td>
<td>-6.7 (-14.6, -2.3)</td>
<td>3.2 (0.9, 7.6)</td>
<td>-9.9 (-18.5, -4.8)</td>
</tr>
<tr>
<td>Massage visits</td>
<td>-2.9 (-5.7, -1.4)</td>
<td>2.6 (-0.4, 8.8)</td>
<td>-5.5 (-12.3, -2.1)</td>
</tr>
<tr>
<td>Physiotherapist visits</td>
<td>-3.6 (-10.3, 0.0)</td>
<td>1.6 (-3.7, 10.0)</td>
<td>-5.2 (-15.4, 1.5)</td>
</tr>
<tr>
<td>Pain medication costs†</td>
<td>-$52 (-$84, -$32)</td>
<td>-$72 (-$277, -$3.5)</td>
<td>$20 (-$53, $219)</td>
</tr>
<tr>
<td>Estimated absenteeism days</td>
<td>-4.8 (-6.2, -3.6)</td>
<td>1.9 (0.9, 3.1)</td>
<td>-6.7 (-8.6, -5.0)</td>
</tr>
</tbody>
</table>

Health-related quality of life (SF-6D, score out of 100) Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Naturopathic care</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>69.7 (10.5)</td>
<td>70.7 (10.2)</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>74.2 (8.2)</td>
<td>72.9 (11.4)</td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>76.4 (9.2)</td>
<td>71.8 (10.2)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>76.9 (11.7)</td>
<td>70.8 (9.5)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>75.9 (11.0)</td>
<td>71.4 (9.6)</td>
<td></td>
</tr>
</tbody>
</table>

*BCa 95% CI indicates bias corrected and accelerated 95% confidence interval.
†Average medication costs rather than pill counts are reported here because of the wide variety of over-the-counter and prescription medications used.

**TABLE 3** Baseline Characteristics of Patients With at Least One Data Collection Point After Treatment Began and for the Control Group Participants With Data Available at 6-month Follow-up*

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Naturopathic care (n=39)</th>
<th>Control (n=31)</th>
<th>Control group participants with 6-month follow-up data (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>45.3 (7.46)</td>
<td>48.2 (8.13)</td>
<td>43.1 (8.84)</td>
</tr>
<tr>
<td>Female, number (%)</td>
<td>22 (56)</td>
<td>13 (42)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Work type/shift, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>19 (49)</td>
<td>10 (32)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Afternoon</td>
<td>5 (13)</td>
<td>7 (23)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Night</td>
<td>5 (13)</td>
<td>9 (29)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Package delivery</td>
<td>8 (21)</td>
<td>2 (6)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Truck driver</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sales representative</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Roland-Morris Disability Questionnaire Score</td>
<td>8.1 (6.09)</td>
<td>5.4 (3.51)</td>
<td>3.6 (3.20)</td>
</tr>
<tr>
<td>Oswestry Disability Index Score</td>
<td>11.9 (8.12)</td>
<td>11.4 (7.70)</td>
<td>8.25 (7.70)</td>
</tr>
<tr>
<td>Baseline quality-adjusted life-year</td>
<td>0.70 (0.105)</td>
<td>0.71 (0.102)</td>
<td>0.74 (0.111)</td>
</tr>
<tr>
<td>Adjunctive care, visits/week Mean (SD); median (range):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractic</td>
<td>0.43 (1.03), 0.0 (0.0 - 4.0)</td>
<td>0.06 (0.16), 0.0 (0.0 - 0.5)</td>
<td>0.03 (0.09), 0.0 (0.0 - 0.3)</td>
</tr>
<tr>
<td>Massage</td>
<td>0.15 (0.32), 0.0 (0.0 - 1.0)</td>
<td>0.17 (0.41), 0.0 (0.0 - 1.5)</td>
<td>0.13 (0.35), 0.0 (0.0 - 1.0)</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>0.28 (0.94), 0.0 (0.0 - 5.0)</td>
<td>0.32 (0.78), 0.0 (0.0 - 3.0)</td>
<td>0.25 (0.46), 0.0 (0.0 - 1.0)</td>
</tr>
<tr>
<td>Pain medication cost/week</td>
<td>$2.72 (4.48); $0.63 ($0.00 - $19.76)</td>
<td>$18.04 (64.63); $0.00 ($0.00 - $274.12)</td>
<td>$34.49 (96.82); $0.00 ($0.00 - $274.12)</td>
</tr>
</tbody>
</table>

*Mean (SD) unless otherwise indicated.
Naturopathic care participants tended to reduce adjunctive care use and have reduced absenteeism. Conversely, control group participants tended to increase adjunctive care (except for medications) and have slightly increased absenteeism. No participant reported adjunctive use of acupuncture. Table 2 also reports HRQoL as measured by the SF-6D. The naturopathic care group experienced a statistically significant ($P=0.006$) increase in QALYs over the 6-month study period, but the control group did not (Table 3). The difference between groups in QALY gains was statistically significant ($P=0.036$). The estimated mean health gain is 0.0256 QALYs, which is equivalent to 9.4 “perfect health” days or to taking average participants’ health (measured by the SF-6D as approximately 70% health at baseline, Table 2) to “perfect health” for 31 days over the 6-month period.

The mean incremental cost to society of naturopathic care is estimated to be -$1212 (a net savings of $1212) per participant (Table 4). Figure 2 shows the cost-utility plane for the societal perspective. The graph represents 1000 bootstrap replications of the relationship between incremental societal costs and incremental QALY gains. All cost-effect pairs (100%) are in the bottom right quadrant, suggesting that naturopathic care is dominant over the control treatment (a standardized physiotherapy education regimen)—that is, the use of naturopathic care instead of the control treatment is associated with both an improvement in HRQoL and lower costs. Under these assumptions and in this population, naturopathic care is a cost-effective alternative to standardized physiotherapy education.

As discussed previously, the portion of these savings that accrues to the employer (through reductions in medical costs, if self-insured, and productivity losses avoided) and the portion that accrues to participants (through out-of-pocket costs avoided) depend upon the coverage limits specified. Table 4 reports the breakdown of adjunctive care costs between the employer and the participant based on employer coverage of 80% of costs up to $400 annually for chiropractic care and massage and up to $1000 for physiotherapy. Medications were covered by this employer at various rates from 0% to 80% with no maximum. Under these assumptions, the majority of the savings due to reductions in adjunctive care accrue to participants as reductions in their out-of-pocket costs.

The other cost that must be allocated before cost-effectiveness to the employer and to the participant can be determined is the cost of treatment. In this study participants in both groups received their treatment at no cost. The employer covered all

![Figure 2 Cost Effectiveness Plane for Societal Costs and Quality-adjusted Life-year (QALY) Gains for Naturopathic Care Compared to the Control Treatment (a standardized physiotherapy regimen) Over 6 Months](image)

### Table 4 Costs (Net of Baseline) and Quality-adjusted Life-years*

<table>
<thead>
<tr>
<th>Costs</th>
<th>Naturopathic care (n=39)</th>
<th>Control (n=31)</th>
<th>Difference (Bootstrap BCa 95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study treatment costs</td>
<td>$1469</td>
<td>$337</td>
<td>$1132</td>
</tr>
<tr>
<td>Adjuvative care costs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiropractic visit costs</td>
<td>-$406 ($1146)</td>
<td>$196 ($561)</td>
<td>-$603 (-$1122, -$292)</td>
</tr>
<tr>
<td>Massage visit costs</td>
<td>-$161 ($350)</td>
<td>$142 ($654)</td>
<td>-$303 (-$677, $116)</td>
</tr>
<tr>
<td>Physiotherapist visit costs</td>
<td>-$221 ($956)</td>
<td>$97 ($1146)</td>
<td>-$318 (-$943, $82)</td>
</tr>
<tr>
<td>Pain medication costs</td>
<td>-$52 ($82)</td>
<td>-$72 ($355)</td>
<td>$20 (-$53, $219)</td>
</tr>
<tr>
<td>Total adjuvative care costs</td>
<td>-$840 ($1828)</td>
<td>$363 ($1272)</td>
<td>-$1203 (-$2097, -$592)</td>
</tr>
<tr>
<td>Estimated productivity loss</td>
<td>-$817 ($758)</td>
<td>$324 ($541)</td>
<td>-$1141 (-$1470, -$866)</td>
</tr>
<tr>
<td><strong>Total Societal Costs</strong></td>
<td>-$188 ($1977)</td>
<td>$1024 ($1456)</td>
<td>-$1212 (-$2169, -$533)</td>
</tr>
<tr>
<td>Adjuvative costs paid by the participant</td>
<td>-$857 ($1783)</td>
<td>$239 ($1022)</td>
<td>-$1086 (-$1959, -$575)</td>
</tr>
<tr>
<td>Adjuvative costs paid by the employer</td>
<td>$17 ($169)</td>
<td>$124 ($430)</td>
<td>-$107 (-$264, $55)</td>
</tr>
<tr>
<td>Quality-adjusted life-years</td>
<td>0.0293 (0.0409)</td>
<td>0.0036 (0.0332)</td>
<td>0.0256 (0.0075, 0.0437)‡</td>
</tr>
</tbody>
</table>

*Mean (SD) unless otherwise indicated.
†BCa 95% CI indicates bias corrected and accelerated 95% confidence interval.
‡95% standard error–based confidence interval.
study costs. Free onsite naturopathic treatment may not necessarily be continued, however, and it should be noted that some of the attractiveness to participants of naturopathic care on this study (possibly affecting retention and outcomes) may have been due to its accessibility and lack of cost.

Assuming that the employer pays all costs of treatment, naturopathic care is cost-effective for participants, with savings in out-of-pocket adjunctive care costs of $1096 and an increase in QALYs of 0.0256. Employer costs of $1025 ($1132 less $107, assuming the employer would also have paid for the control treatment) are compared to a net reduction in absenteeism days of 6.7 (95% CI: -4.8, -8.6) for an incremental cost-effectiveness ratio for the employer of $154 per absentee day avoided. If employer costs per absentee day are $172 ($21.44 per hour times 8 hours) as assumed in this analysis, then under the assumptions of this study, offering naturopathic care is a cost-effective alternative to standardized physiotherapy education to employers. Comparing an investment of $1469 for naturopathic care per participant to a return of $1585 ($337 + $107 + $1141) gives a return on investment over the 6 months of 7.9%.

Sensitivity analyses indicate that the incremental societal cost savings shown in this study are robust to widely differing cost and resource use assumptions. Varying each resource use category across its 95% confidence interval range and varying unit prices from 50% to 150% in all cases generated incremental societal cost savings. The largest changes in societal costs came from varying the cost of the naturopathic care visits (incremental societal costs ranged from -$1948 to -$479), varying labor costs (incremental societal costs ranged from -$1784 to -$643), and varying the number of adjunctive care physiotherapy visits (incremental societal costs ranged from -$1838 to -$803). However, if absenteeism costs (productivity losses) are not counted or realized, incremental societal cost savings drop to near 0 (Table 5). Nevertheless, naturopathic care would still be considered to be the cost-effective alternative to standardized physiotherapy education to employers. Because of the large number of unavailable data for the control group, mainly at the 6-month follow-up, total societal costs and QALY gains were calculated including only those participants who did not take the crossover naturopathic treatment option and who reported 6-month data. Comparing results for the naturopathic care group in Table 5 to those shown in Table 4, as expected due to the small number of this group lost to follow-up, there is not much change in their total societal costs (an average of -$192 for those reporting 6-month data compared to -$188 for the full sample) or QALYs (an average of 0.0263 for those reporting 6-month data compared to 0.0293 for the full sample). It seems that those in the naturopathic group who did not provide 6-month data were doing somewhat better health-wise (QALYs, when they are included, are higher) and were almost identical on costs to those who provided data. The control group participants who took crossover naturopathic treatment and/or who did not provide 6-month data were doing worse health-wise (average QALYs decrease from 0.0110 to 0.0036 when they are included) and had higher costs (average societal costs increase from $666 to $1024 when they are included) than those who did not cross over but did provide 6-month data. Therefore, those lost to 6-month follow-up in the naturopathic group were doing better than average and those lost to 6-month follow-up in the control group were doing worse than average in terms of both HRQoL and costs. Control group participants who did not take crossover care and did provide 6-month data also were in better health at baseline than control participants who opted for crossover naturopathic care (Table 3).

### DISCUSSION

Naturopathic care for the treatment of chronic low back pain in this population of warehouse workers is a cost-effective alternative to a standardized physiotherapy education regimen from a societal perspective. Naturopathic care resulted in significantly lower societal costs and significantly better HRQoL than the control treatment over the 3-month treatment period and 3-month follow-up. Naturopathic care was also cost-effective to the employer and participants under the coverage assumptions used in this study. This is the first economic evaluation of naturopathic medicine and one of the first of a package of care including complementary and alternative medicine therapies.²² Naturopathic care for the treatment of chronic low back pain in this population of warehouse workers is a cost-effective alternative to a standardized physiotherapy education regimen from a societal perspective. Naturopathic care resulted in significantly lower societal costs and significantly better HRQoL than the control treatment over the 3-month treatment period and 3-month follow-up. Naturopathic care was also cost-effective to the employer and participants under the coverage assumptions used in this study. This is the first economic evaluation of naturopathic medicine and one of the first of a package of care including complementary and alternative medicine therapies.

### TABLE 5 Sensitivity Analysis*

<table>
<thead>
<tr>
<th>Sensitivity analysis scenarios</th>
<th>Naturopathic care (n=39)</th>
<th>Control (n=31)</th>
<th>Difference (Bootstrap BCa 95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism excluded</td>
<td>$629 ($1828)</td>
<td>$700 ($1272)</td>
<td>-$71 ($965, $540)</td>
</tr>
<tr>
<td>Absenteeism at higher rate</td>
<td>-$635 ($2170)</td>
<td>$1202 ($1625)</td>
<td>-$1836 ($2886, $1058)</td>
</tr>
<tr>
<td>Analysis using only those participants that reported 6-month data‡</td>
<td>$192 ($2135)</td>
<td>$666 ($1652)</td>
<td>-$858 ($2564, $123)</td>
</tr>
<tr>
<td>Total societal costs</td>
<td>0.0263 (0.0434)</td>
<td>0.0110 (0.0348)</td>
<td>0.0153 (-0.0182, 0.0488)§</td>
</tr>
</tbody>
</table>

*Mean (SD) unless otherwise indicated.
†BCa 95% CI indicates bias corrected and accelerated 95% confidence interval.
‡Naturopathic care (n=32), control (n=8).
§95% standard error–based confidence interval.
medicine is practiced as a system of medicine, not as individual therapies. Therefore, it is appropriate that multiple therapies (here acupuncture, exercise and dietary advice, relaxation training, and a back care education booklet) applied by trained naturopathic physicians be included in an evaluation of naturopathic medicine. However, this study falls short of an evaluation of the system of naturopathic medicine in that the physicians were restricted to these modalities in their treatment of patients.

Although this study followed published guidelines for economic evaluations, it is not without limitations, and as with any economic evaluation, the generalizability of the results depends on the assumptions made. For example, there are a number of factors that could improve the cost-effectiveness of naturopathic care for low back pain offered in other settings. This study did not measure "presenteeism" (productivity at work) impacts, which could significantly increase the savings in productivity due to the intervention. In one study, workers who reported chronic back or neck disorders as their primary condition also reported an average reduction of 21.7% over the last month in their at-work productivity. Similarly, if reductions in lost leisure time follow the same pattern as work-related productivity losses, the inclusion of the value of quality leisure time regained would also increase cost-effectiveness. The duration of the intervention also could be shortened to reduce intervention costs. A recently completed growth curve analysis of the trial data indicates that although a 3-month intervention period was used in this study, the full health benefits of the intervention could be achieved after 2 months, and the health benefits of naturopathic care are maintained at a constant level for the duration of the 3-month follow-up (Herman and Sechrest, in preparation). If impacts continue past 6 months, cost-effectiveness analyses taking this longer period of benefits into account would show an even greater increase in health benefits in terms of QALYs.

There are also a number of factors that could reduce the cost-effectiveness of naturopathic care. Because this study used an onsite clinic to provide care during work hours, there were no travel, time-off-work, or child-care costs for visits. Inclusion of these costs would likely decrease cost-effectiveness. The same 2 naturopathic physicians offered both the naturopathic care and control group treatment. It is possible that they unconsciously negatively biased the results of the control group. Lack of blinding also may have negatively biased the results of the control group, especially since this was a sample of workers who volunteered for a study of naturopathic care, albeit with the forewarning that they may not be randomized to the naturopathic care group. Participants seemed to show a strong preference for naturopathic care—all immediate post-randomization dropouts were from the control group, and 42% of those remaining at 3 months took advantage of the offer of crossover naturopathic care. Retention in the naturopathic care group was excellent (82% at 6-month follow-up), and the participants who left the study, possibly due to time constraints, tended to be those with the better health outcomes. In the control group the non-completers and those taking advantage of the crossover tended to be those with worse health outcomes. A pre-randomization measure of patient preferences may have provided some insight into these results.

Other limitations include the small sample size, the unavoidable reduction in follow-up data for the control group due to the popularity of the naturopathic care crossover offer, the lack of a direct measure of absenteeism, and the limits on generalizability that come from recruiting all participants from 1 worksite.

CONCLUSIONS

This economic evaluation alongside a pragmatic randomized control trial shows naturopathic care to be more cost-effective than a standardized physiotherapy education regimen in the treatment of chronic low back pain from the societal, employer, and participant perspectives. Further studies of the economic impact of naturopathic medicine are warranted, especially those that address the limitations of this study.

Acknowledgments

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REFERENCES


“Mauve Factor” was once mistaken for kryptopyrrole but is the hydroxylactam of hemopyrrole, hydroxyhemopyrrolin-2-one (HPL). Treatment with nutrients—particularly vitamin B₆ and zinc—reduces urinary excretion of HPL and improves diverse neurobehavioral symptoms in subjects with elevated urinary HPL. Heightened HPL excretion classically associates with emotional stress, which in turn is known to associate with oxidative stress. For this review, markers for nutritional status and for oxidative stress were examined in relationship to urinary HPL.

In cohorts with mixed diagnoses, 24-hour urinary HPL correlated negatively with vitamin B₆ activity and zinc concentration in red cells (P<.0001). Above-normal HPL excretion corresponded to subnormal vitamin B₆ activity and subnormal zinc with remarkable consistency. HPL correlated inversely with plasma glutathione and red-cell catalase, and correlated directly with plasma nitric oxide (P<.0001). Thus, besides implying proportionate needs for vitamin B₆ and zinc, HPL is a promising biomarker for oxidative stress. HPL is known to cause non-erythroid heme depression, which lowers zinc, increases nitric oxide, and increases oxidative stress.

Administration of prednisone reportedly provoked HPL excretion in animals. Since adrenocorticotid (and catecholamine) stress hormones mediate intestinal permeability, urinary HPL was examined in relationship to urinary indicans, presumptive marker for intestinal permeability. Urinary HPL associated with higher levels of indicans (P<.0001). Antibiotics reportedly reduce HPL in urine, suggesting an enterobiotic role in production. Potentially, gut is a reservoir for HPL or its precursor, and stress-related changes in intestinal permeability mediate systemic and urinary concentrations.

Editor’s note: The following is part 1 of a 2-part article. Part 2 will appear in the May/Jun 2008 issue of Alternative Therapies in Health and Medicine.

“Mauve Factor,” or “Mauve” (mōv) for brevity, first was detected in the urine of psychiatric patients by the Hoffer group in 1958 and named for its appearance on paper chromatograms. Irvine extracted the compound from urine, correctly assigned the structure to the pyrrole family, and conferred the common name. Early technology permitted only qualitative assay.

Hoffer observed that recovery from acute schizophrenia associated with disappearance of Mauve from the urine, regression with reappearances. Large doses of vitamin B₆ suppressed Mauve in schizophrenics. Pfeiffer reported superior clinical results with combined vitamin B₆ and zinc, which suppressed Mauve and improved symptoms in many neurobehavioral disorders.

The Pfeiffer group introduced a colorimetric quantitative assay for Mauve, which utilizes kryptopyrrole (KP) as standard. Structural similarity affords the use of KP as standard. HPL assay, but the 2 molecules are distinct (Figure 1). Mauve was identified mistakenly as KP by Irvine in a high-profile scientific journal in 1969 and again by Sohler in 1970. A flurry of research on the experimental effects of KP eventuated. Improved technology demonstrated that KP is not found in human urine, and Mauve was identified indisputably by synthesis as HPL. “HPL” and “Mauve” are used synonymously in this article and
Discerning the Mauve Factor, Part 1

for clarity may be substituted for erroneous use of “kryptopyrrole” in older documents. “High-Mauve” denotes subjects or groups with elevated HPL or with a tendency to excrete excess HPL. “Pyrroluria” lacks specificity, as many pyrroles appear in urine. HPL is unstable outside the body, readily interconverting with other structures. Exposure to light or to seemingly mild chemical treatments reduces detectable HPL, which also is acid labile (a study that unadvisedly used hydrochloric acid to preserve urine failed to detect HPL in schizophrenia, a condition well known for HPL elevation). Graham reported the half-life of HPL in urine at room temperature to be 10 to 12 hours, although the extent of light exposure was unspecified.

Addition of ascorbate preservative and protection from light and heat maximize detection of HPL. Besides light-shielding transport tubes, one laboratory (Vitamin Diagnostics, Cliffwood Beach, New Jersey) recommends urine collection under dim light and employs darkroom assay conditions. If assay for HPL cannot be performed immediately, overnight shipment and/or freezing of the urine sample are required by all North American laboratories surveyed for this review. Gorchein found that freezing to -8º C stabilized HPL in urine for up to 4 months. Re-freezing of thawed specimens diminishes detectable HPL (Ellen Hanson, Laboratory Supervisor, Direct Health Care Access II Laboratory, Inc, Mount Prospect, Illinois; oral communication, September 2006).

KP is readily oxidized, so laboratories take special precautions to maintain purity of KP used for colorimetric HPL assay. Occasionally, the colorimetric assay is invalidated by the presence of other Ehrlich-reactive compounds which produce spectrophotometric interference at 540 nm. Urobilinogen is the most common offender. Others reportedly include hemoglobin, bilirubin, and mendelamine (oral communication, September 2006, from Irwin Sommerfeld, Laboratory Director of Direct Health Care Access II Laboratory).

VALIDATION OF THE COLORIMETRIC ASSAY FOR URINARY HPL

HPL assay utilizing high-pressure liquid chromatography/mass spectroscopy (HPLC/MS) and synthetic HPL standard is highly sensitive and specific. In a comparison of split-urine samples by Vitamin Diagnostics Laboratory, the simpler colorimetric assay for HPL correlated very highly with HPLC/MS (r=0.98; P<.0001) (Figure 2). It should be noted that absolute HPL values varied on the 2 assays. The normal range for colorimetric assay was <15 µg/dL, but for MS/HPLC, normal was <25 µg/dL. The latter compares favorably with Graham’s normal range of <26 µg/dL utilizing gas-liquid chromatography and synthetic HPL standard.

EFFECTS OF VARIABLE HYDRATION ON HPL CONCENTRATION

Normalization of values to urinary specific gravity (SG) or creatinine corrects for variable hydration. Pfeiffer encouraged normalization of the colorimetric assay to SG in his later years, according to Tapan Audhya, PhD (oral communication, June 2006). Examination of results from 600 colorimetric assays from the BioCenter Laboratory in Wichita, Kansas, revealed that 20% of HPL values moved into or out of the normal range after adjustment to SG by refractometry. Examination of data from the BioCenter Laboratory and from the Direct Health Care Access II Laboratory revealed that normalization affects reported HPL values up to 4-fold.

Normalization was found to improve correlation with other laboratory parameters. Before normalization to SG, HPL in single-void specimens from subjects with mixed diagnoses failed to correlate significantly with plasma zinc (N=87; r=-0.15; P=.18). In written communication from July 2006, William Walsh, PhD, reported that significant correlations were achieved after normalization of colorimetric HPL to SG (r=-0.28, P=.009) and to creatinine (r=-0.30, P=.004). Graham’s peer-reviewed publications adjusted HPL to creatinine.

Addition of ascorbate to urine collections protects HPL from
Mauve Excretion Patterns

In most cases, day-to-day deviations around a baseline mean do not preclude identification of subjects prone to HPL elevation. Sporadic spikes in HPL well above baseline associate with stress, as will be discussed later. There is evidence that HPL excretion can increase very rapidly. In 1992, a study for the US Navy measured urinary HPL (colorimetric, normalized to SG) after male volunteers were subjected to brief cold-water immersion stress. In an oral summary of the study, Tapan Audhya, PhD, reported that whole blood levels for HPL (2-dimensional thin-layer chromatography, synthetic HPL standard) ranged between 4 and 10 μg/dL. Dialysis cleared HPL from both blood and urine.

Interfering substances have frustrated efforts to develop a practical blood test for HPL.

HPL AND STRESS

O'Reilly hypothesized that Mauve excretion increases during

<table>
<thead>
<tr>
<th>TABLE 1 Neurobehavioral Disorders Associated With Elevated HPL*</th>
<th>Percentage High-Mauve</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>100</td>
</tr>
<tr>
<td>Latent AIP*</td>
<td>70</td>
</tr>
<tr>
<td>Down syndrome*</td>
<td>71</td>
</tr>
<tr>
<td>Schizophrenia, acute*</td>
<td>59-80</td>
</tr>
<tr>
<td>Schizophrenia, chronic*</td>
<td>40-50</td>
</tr>
<tr>
<td>Criminal behavior</td>
<td></td>
</tr>
<tr>
<td>Adults, sudden deviance*</td>
<td>71</td>
</tr>
<tr>
<td>Youths, violent offenders*</td>
<td>33</td>
</tr>
<tr>
<td>Manic depression*</td>
<td>47-50</td>
</tr>
<tr>
<td>Depression, non-schizophrenic*</td>
<td>12-46</td>
</tr>
<tr>
<td>Autism*</td>
<td>46-48</td>
</tr>
<tr>
<td>Epilepsy*</td>
<td>44</td>
</tr>
<tr>
<td>Learning disability/ADHD*</td>
<td>40-47</td>
</tr>
<tr>
<td>Neuroses*</td>
<td>20</td>
</tr>
<tr>
<td>Alcoholism*</td>
<td>20-84</td>
</tr>
</tbody>
</table>

* AIP indicates acute intermittent porphyria; ADHD, attention deficit hyperactivity disorder.
Discerning the Mauve Factor, Part 1

VITAMIN B₆ AND ZINC

Pfeiffer discovered the clinical response of high-Mauve subjects to B₆ and zinc in 1971 and saw remarkable improvements in a series of 1000 high-Mauve patients.¹⁶,⁷¹

Treatment with B₆ and zinc reportedly reduced mean urinary HPL in 99 patients from 60 μg/dL to 30 μg/dL in 1 month.²⁰ Although randomized trials have not been performed, combined B₆ and zinc are now entrenched as core treatment for high-Mauve subjects during physical or emotional stress.⁴⁶ Clinicians give higher short-term “stress doses” of both B₆ and zinc.¹⁶,⁷⁰

Clinicians report proportionality between Mauve excretion and symptom severity²⁰ and according to the late Hugh Riordan, MD, former director of the Center for the Improvement of Human Functioning International, Wichita, Kansas (oral communication, 2000), higher Mauve excretion usually requires higher dosages of B₆ and zinc for suppression. HPL in urine decreased progressively with higher B₆ dosing,³⁶ and progressive B₆ dosing associates with normalization of erythrocyte glutamate oxaloacetate transaminase (EGOT).⁷²

Initially, Pfeiffer tended to use high doses of vitamin B₆ (400-3000 mg daily) and relatively modest (“dietary”) doses of zinc. Later, some patients were noted to respond optimally to B₆ and as much as 160 mg daily of elemental zinc.¹³,¹⁶,⁷³,⁷⁵ Pfeiffer reported that on occasion, previously high-Mauve subjects no longer may require high doses of B₆ and zinc ¹⁶; the phe-

The data affirm HPL as biomarker for functional B₆ deficiency and zinc deficiency in high-Mauve subjects results from increased urinary loss of P5P and zinc due to complexation with Mauve, and they cited 20 μg/dL higher zinc content in spot urines of Mauve-positive subjects.¹³ The finding would extrapolate to relatively insubstantial total zinc loss, unless the effect extended to other routes of excretion. Pfeiffer published evidence of binding between P5P and KP¹⁰ and between zinc and KP²⁰ but did not study HPL.

The original data presented in this review were retrieved retroactively and anonymously from laboratory records, without regard to primary diagnosis or other criteria. In samples collected at the Biolab Medical Unit, London, colorimetric urinary HPL (single-void, unadjusted to SG or creatinine), correlated moderately with EGOT (n=58; r=–0.42; P=.001). In samples collected at the Vitamin Diagnostic Laboratory, HPL by HPLC/MS in 24-hour urines, normalized to SG, correlated strongly with EGOT (n=32; r=–0.77; P<.0001); all 24 subjects with abnormal HPL had below-normal or borderline-low EGOT (Figure 3).

Pfeiffer and Sohler proposed that functional B₆ deficiency and zinc deficiency in high-Mauve subjects results from increased urinary loss of P5P and zinc due to complexation with Mauve, and they cited 20 μg/dL higher zinc content in spot urines of Mauve-positive subjects.¹³ The finding would extrapolate to relatively insubstantial total zinc loss, unless the effect extended to other routes of excretion. Pfeiffer published evidence of binding between P5P and KP¹⁰ and between zinc and KP²⁰ but did not study HPL.

Validation of HPL as a Marker for B₆ Status

The data affirm HPL as biomarker for functional B₆ deficiency and zinc deficiency in high-Mauve subjects results from increased urinary loss of P5P and zinc due to complexation with Mauve, and they cited 20 μg/dL higher zinc content in spot urines of Mauve-positive subjects.¹³ The finding would extrapolate to relatively insubstantial total zinc loss, unless the effect extended to other routes of excretion. Pfeiffer published evidence of binding between P5P and KP¹⁰ and between zinc and KP²⁰ but did not study HPL.
Validation of HPL as a Marker for Zinc Status

White flecks in the nails (Figure 4) are responsive to zinc16,71,76 and reportedly detectable in 60% of high-Mauve subjects. HPL was examined in relationship to 3 different measurements for zinc. As discussed earlier, Walsh reported that plasma zinc and single-void colorimetric HPL correlated significantly once normalized to SG (r=–0.28; P=.009) or to creatinine (r=–0.30; P=.004).

Cellular zinc levels correlated more strongly with urinary HPL. In samples at the BioLab Medical Unit, single-void colorimetric HPL (unadjusted to SG) from a mixed cohort correlated substantially with white-cell zinc (N=58; r=–0.60; P<.0001). Abnormal HPL corresponded to below-normal white-cell zinc in 42 of 58 patients (Figure 5). In samples at Vitamin Diagnostic Laboratory, stronger association existed between red-cell zinc and 24-hour urinary HPL (HPLC/MS, adjusted to SG) in a mixed cohort (N=37; r=–0.88; P<.0001). Twenty-four of 24 subjects with elevated HPL had below-normal red-cell zinc (Figure 6).

TABLE 2 Signs, Symptoms, and Traits Clinicians Report as More Prevalent in High-Mauve Patients

<table>
<thead>
<tr>
<th>Poor dream recall</th>
<th>Impotence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail spots</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Stretch marks (striae)</td>
<td>B6-responsive anemia</td>
</tr>
<tr>
<td>Pale skin/poor tanning</td>
<td>Attention deficit/hyperactivity</td>
</tr>
<tr>
<td>Coarse eyebrows</td>
<td>Crime and delinquency</td>
</tr>
<tr>
<td>Knee and joint pain</td>
<td>Substance abuse</td>
</tr>
<tr>
<td>Acne</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Allergy</td>
<td>Stress intolerance</td>
</tr>
<tr>
<td>Cold hands or feet</td>
<td>Emotional lability</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>Explosive anger</td>
</tr>
<tr>
<td>Stitch in side</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Constipation</td>
<td>Pessimism</td>
</tr>
<tr>
<td>Morning nausea</td>
<td>Dyslexia</td>
</tr>
<tr>
<td>Light/sound/odor intolerance</td>
<td>Familial or social withdrawal</td>
</tr>
<tr>
<td>Tremor/shaking/spasms</td>
<td>Depression</td>
</tr>
<tr>
<td>Hypoglycemia/glucose intolerance</td>
<td>Paranoia</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Migraine</td>
<td>Disordered perception</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Amenorrhea/irregular periods</td>
<td>Autism</td>
</tr>
</tbody>
</table>

*The frequency of these features and their relationship to biochemical abnormalities associated with HPL are not well-studied.

**FIGURE 4** Leukodynia Implies Zinc Deficit

In this high-Mauve subject, white flecks in nails resolved after institution of 100 mg of elemental zinc daily, reoccurred after dosage was lowered to 40 mg, and again abated on higher dosage.

**FIGURE 5** Single-void HPL and White-cell Zinc

Colorimetric HPL equivalents in single-void urines, unadjusted to specific gravity, correlates with white-cell zinc in mixed cohort. Normal values: HPL <8 μg/dL; white-cell zinc > 5.4 ng/106 leukocytes. N=58; r=–0.60; P<.0001.
As a class, pyrroles have been called "nerve poisons."80 HPL is from the subclass of monopyrroles, well known for biotoxicity.3,45 Batrachotoxin (poison-dart frog)81 and PBG82 are monopyrroles which exert potent effects on the nervous system. KP3,10,22,24,25,29,31-33,45,83 and the hydroxylactam of kryptopyrrole (KPL),84,85 highly homolo-

gous to HPL, cause acute neurobehavioral effects in animals. Structural similarity of HPL to pyroglutamate and kainic acid41 suggests possible direct effects on neurotransmission. 

Irvine produced ptosis, locomotor abnormalities, and hypothermia in rats with unspecified doses of HPL.86 Cutler found that intraperitoneal injection of HPL 0.65 μmol/kg produced relatively mild acute effects: decreased gross activity, increased preference for light areas of the cage, and a trend toward more aggressive behavior. A higher dose of 1.95 μmol/kg increased head-twitch and backward locomotion,41 behaviors seen in rats treated with hallucinogens.87

Strictly by estimation, Cutler discounted significant behavioral effects in humans from HPL, because the plasma concentration of 0.3 μmol/kg (equivalent to 4.6 μg/dL) achieved in rats with the higher dose of HPL was adjudged "many-fold" greater than plausible HPL blood levels in humans.41 The estimation overlooked published data from Semmelweiss Medical University, which reported a whole-blood range for HPL of 4 to 10 μg/dL in schizophrenics.54 Cutler’s higher dose of HPL marginally achieved this range.

HPL definitely is porphyrinogenic in animals. Cutler’s lower dose of HPL significantly increased total urinary porphyrin excretion in rats.52,85,88 Graham documented peak urinary HPL immediately prior to a severe attack of acute intermittent porphyria (AIP),39 but alteration of porphyrin metabolism by HPL has not been proven in humans. Nevertheless, elevation of HPL in the porphyrias is well documented.22,32,89-93 In AIP, HPL is elevated consistently and during AIP neurovisceral crisis may reach urinary concentration as high as 946 μg/dL.90 In AIP—including the latent state—HPL consistently associates with urinary PBG and ALA.52,93

The association of HPL with ALA is not limited to AIP. In a mixed group of psychiatric patients (N=128), urinary HPL and ALA correlated positively.94 ALA is a potent oxidant and neurotoxin95 with known effects on neuronal energy production96 and neurotransmission.97,98 ALA binds P5P and produces free radicals by autooxidation.99 Animal studies that failed to increase ALA after injection with HPL88 used the Cutler doses.

Ex vivo, guinea-pig ileal contractions were inhibited by HPL at seemingly high concentrations of 8.5 μmol/kg (132 μg/dL),90 but HPL in human bowel or stool has not been quantified for reference.

HPL DEPRESSES HEME

Heme is tightly coupled to neuronal metabolic activity.101 Depression of heme leads to metabolic crisis, with mitochondrial102 and neuronal103 decay. Injection of rats with Cutler’s lower dose (0.65 μmol/kg) of HPL at 0 and 24 hours reduced hepatic microsomal heme (by 42%) and heme-containing cytochrome P-450 (by 55%) at 48 hours.101 Equivalent reduction of heme in cultured neurons with N-methylprotoporphyrin IX (NMP) reduces mitochondrial complex IV, upregulates nitric oxide synthase (NOS), and reduces intracellular zinc by half.101 NMP inhibits heme synthesis, the proposed mechanism for HPL.52,93 It is possible that HPL directly binds heme, as does KPL in vitro.104
Non-erythroid heme in high-Mauve subjects has not been measured, but depressed levels are predictable. Besides potential depression by HPL, deficiencies of zinc, B6, and biotin (all cofactors for heme synthesis) independently decrease non-erythroid heme.110-112 And heme is degraded by stress.112 It should be mentioned as well that heavy metals, which have not been examined in relation to Mauve, are renowned dysregulators of porphyrin metabolism and increase heme degradation.112

Heme plays a central role in energy production and is required by a family of biomolecules needed for detoxification and antioxidant defense: catalase, cystathionine synthase, cytochrome P450, guanylate cyclase, heme-hemopexin (for production of metallothionein), NOS, pyrrolase, sulfite reductase. Ultimately, heme depression increases oxidant leak from mitochondria and oxidative damage to cells.106

HPL AND OXIDATIVE STRESS

Oxidative stress clearly results from deficiency of zinc or B6, as reviewed by McGinnis.105 For example, even marginal B6 deficiency is associated with lower glutathione peroxidase (GSHPx), lower glutathione (GSH) reductase, lower reduced/oxidized glutathione ratios, higher lipid peroxide levels, and mitochondrial decay.106-108 The B6 vitamers are themselves highly vulnerable to damage by oxidative species.109-111 P5P protects neurons from oxidative stress, apparently by increasing energy production and lowering excitotoxicity,112,113 and zinc supplementation decreases oxidized biomolecules.114,115 Since HPL is a marker for B6 and zinc deficiency, HPL is a potential biomarker for oxidative stress.

Biomarkers for oxidative stress are known to be higher in high-Mauve disorders such as schizophrenia,116 autism,117-119 ADHD,120 Down syndrome,121-123 and alcoholism.124,125 In schizophrenia, lower blood levels of glutathione and response to intravenous glutathione were reported nearly 50 years ago.126

Plasma levels of reduced GSH, the ubiquitous intracellular antioxidant, are decreased in diseases associated with greater oxidative stress,126 including Down syndrome.123 In Alzheimer’s disease, in which oxidative modification of brain precedes appearance of neurofibrillary tangles and plaque,123,124 plasma GSH correlates inversely with brain levels of oxidatively-modified biomolecules.114 It is reasonable to view plasma GSH as a biomarker for pathological effects of oxidative stress.

Initial data from a small cohort of Austrian patients with mixed diagnoses suggested an association between urinary HPL and plasma GSH. Peter Lauda, MD, reported that single-void colorimetric HPL, adjusted to creatinine, correlated modestly with red-cell GSH (r=-0.41) in a group of patients in whom HPL was elevated only in 1 of 13 subjects (written communication, 2005). In samples from the Vitamin Diagnostics Laboratory, 24-hour urinary HPL correlates with plasma GSH in a mixed cohort (Figure 8). In addition to proposed direct effects of HPL on heme synthesis, depression of catalase may result from greater oxidative stress in high-Mauve subjects, because catalase is sensitive to oxidative degradation117 (as is GSHPx,138 which also can remove H2O2 in a reaction using GSH as substrate).119

Depressed catalase hypothetically predisposes high-Mauve subjects to excess H2O2, a freely-diffusible and potent oxidant. Catalase consists of 4 protein subunits, each requiring a heme group. Since catalase requires heme and HPL suppresses heme, it follows that HPL may associate with lower catalase. Lower catalase in blood is reported in schizophrenia105,110 and autism.130

In samples collected at the Vitamin Diagnostics Laboratory, red-cell catalase activity in a mixed cohort was found to correlate inversely with 24-hour urinary HPL by HPLC/MS, normalized to SG (N=30; r=-0.92, P<.0001). Abnormal HPL corresponded to subnormal catalase in 15 of 17 subjects (Figure 9). In addition to proposed direct effects of HPL on heme synthesis, depression of catalase may result from greater oxidative stress in high-Mauve subjects, because catalase is sensitive to oxidative degradation117 (as is GSHPx,138 which also can remove H2O2 in a reaction using GSH as substrate).119

Depressed catalase hypothetically predisposes high-Mauve subjects to excess H2O2 and presents a possible explanation for hypopigmentation of skin associated with Mauve—including, in the extreme, classic “china-doll” complexion.10,11 The pathogenesis of vitiligo illuminates the effect of abnormal catalase and H2O2 on pigmentation. A genetic polymorphism for catalase apparently predisposes patients to vitiligo.140 All patients with vitiligo exhibit decreased catalase and increased H2O2 in epidermis.141 In the presence of excess H2O2, melanocytes142 and melatonin (which normally functions to bind redox-active metals and thereby reduce oxidative stress) are damaged, resulting in lesser pigment production.143 If destruction of melanocytes by excess H2O2 is not complete, treatment with pseudo-catalase restores skin pigmentation by reducing H2O2.144,145

HPL AND CATALASE

Catalase is an endogenous antioxidant that prevents excess cellular hydrogen peroxide (H2O2), a freely-diffusible and potent oxidant. Catalase consists of 4 protein subunits, each requiring a heme group. Since catalase requires heme and HPL suppresses heme, it follows that HPL may associate with lower catalase. Lower catalase in blood is reported in schizophrenia105,110 and autism.130
As stress classically associates with Mauve, so do stressful life events associate with the onset of vitiligo. Catecholamines, which increase as a consequence of stress, are increased in vitiligo patients, particularly during the active phase. Both the synthesis of catecholamines and their auto-oxidation produce H$_2$O$_2$. Catecholamine excess is cytotoxic in diverse tissues, and the toxicity is oxidatively mediated by H$_2$O$_2$. Excess is implicated clearly in human heart disease, and cardiomyocyte apoptosis produced by catecholamine infusion is prevented by antioxidant vitamins. In cultured neurons, toxicity of epinephrine and norepinephrine is reproduced by addition of equimolar H$_2$O$_2$ or blocked completely by addition of catalase. Catecholamine excess in neurobehavior was anticipated by Abram Hoffer in the Adrenochrome Hypothesis of Schizophrenia in 1954.

Besides lighter skin, lighter hair coloration than siblings and earlier gray is reported in high-Mauve subjects. Excess H$_2$O$_2$ is known to increase proportions of oxymelanin in hair, with lightening analogous to the effect achieved by topical application of bleach for cosmetic purposes. Excess H$_2$O$_2$ remains hypothetical until levels are measured in the high-Mauve population. Zinc deficiency alone may explain hypopigmentation associated with Mauve. Melanin is rich in zinc and requires zinc for synthesis and maintenance. Zinc protects melanocytes from oxidation, and zinc-deficiency grays the coats of rats. Oxidants, including H$_2$O$_2$, displace zinc from binding proteins, and it has been suggested that clinical zinc depletion results inherently from greater oxidative stress.

**HPL AND NITRIC OXIDE**

Heme depression results in excess nitric oxide (NO), which is injurious to the brain and is suspected to play a role in such high-Mauve disorders as schizophrenia, autism, and Down syndrome. In schizophrenia and autism, stable metabolites of NO are elevated in conjunction with greater thiobarbituric acid-reactive substances in plasma.

In samples from a mixed cohort at Vitamin Diagnostics Laboratory, plasma NO, measured directly, and 24-hour urinary HPL by HPLC/MS, normalized to SG, correlated positively (N=30; r=0.60; P<0.001). The statistical relationship strengthens substantially (r=0.96) if an extreme outlier is excluded on the presumption of poor sample preservation (Figure 10). The strong association with NO enhances Mauve as a biomarker for oxidative stress.

**FIGURE 9** HPL and Red-cell Catalase

HPL by high-pressure liquid chromatography/mass spectroscopy in 24-hour urine correlates with red-cell catalase in mixed cohort. Normal values: HPL < 25 μg/dL; red-cell catalase >130 units/min/mg of hemoglobin. N=30, r=–0.92; P<0.001.

**FIGURE 10** HPL and Plasma Nitric Oxide

HPL by mass spectroscopy/high-pressure liquid chromatography in 24-hour urine correlates with plasma nitric oxide in mixed cohort. Normal values: HPL<25 μg/dL; plasma nitric oxide 18-36 μmol/L. N=30; r=0.60; with exclusion of an extreme outlier (6.4, 186), r=0.97, P<0.001.

It should be noted that while altered functional B$_6$, zinc, biotin, GSH, catalase, and NO all point toward increased oxidative stress in association with urinary HPL, the data presented are from non-congruent cohorts. Proof that these parameters move together would require same-subject measurement of each.

**Acknowledgments**

The authors wish to acknowledge Nina A. Mikirova, PhD, Bio-Communications Research Institute, Wichita, Kansas, for statistical analysis of data presented in this report and Jackson County Library Services, Jackson County, Oregon, for documentary support.

**REFERENCES**


ISOLATES ARE NOT A LIVING FORCE
Incredibly, 99% of “pure” and “whole food” professional supplements lack actives intrinsic within live foods.

OF ALL PROFESSIONAL SUPPLEMENTS:

96% ARE “PURE”

“Pure” vitamin C is a fractionated crystalline compound, synthesized from refined corn syrup or sugar, and not from food. Delivered as an isolated vitamin, “pure” or hypoallergenic vitamin C is devoid of the synergistic constituents required for nutrient utilization within the physiology. Active constituents are inherent only in whole plant materials; they cannot be re-created in a lab. Thus, “pure” vitamin C devoid of active constituents cannot support life because they are chemicals with no food value.

Ascorbic acid and calcium ascorbate are two common hypoallergenic forms of “pure” vitamin C. This NMR photo of “pure” ascorbic acid powder clearly depicts a static and crystalline pattern, properties characteristic of a non-living system.

3% ARE “WHOLE FOOD”

In many cases, “whole food” supplements have shown better rates of utilization than “pure” supplements. However, due to processing, they lack the full nutritional potential and activity of the original whole food. This processing will inevitably denature proteins, destroy constituents, and decrease the potency of these nutrients, nullifying the components of food which cannot be replaced.

This NMR photo is of a “whole food” vitamin C supplement. The photo shows how the processing methods used to create “whole food” supplements radically disrupts the food’s matrix. With the food attachments now destroyed, the remaining constituents form a multitude of self-similar spheres existing independently of each other and no longer as a cohesive dynamic system.

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This NMR photo is of vitamin C from Innate Response Formulas™; it captures the fluid and dynamic properties of this unique raw material. Note the continuum of self-similar cellular components, each in a different phase of replication and transformation, phenomena indicative of a living system. Vitamin C in a native state has the actives to help actualize an innate healing response within the physiology.

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“Purified” Magnetic Resonance (NMR) groups taken at Florida State University capture the true essence of vitamins at the molecular level. ©2003

The True Actives of Live Foods
Green Tea of the Future • Flax Seed • Cumin • Blessed Herb Whole

INCREASING RESEARCH CAPACITY AT THE NEW ENGLAND SCHOOL OF ACUPUNCTURE THROUGH FACULTY AND STUDENT RESEARCH TRAINING INITIATIVES

Peter M. Wayne, PhD; Julie E. Buring, ScD; Roger B. Davis, ScD; Sally M. Andrews, MBA; Meredith St John, LicAc; Lisa Conboy, ScD; Catherine E. Kerr, PhD; Ted J. Kaptchuk, OMD; Steven C. Schachter, MD

Few complementary and alternative medicine (CAM) institutions require their students to undergo substantive training in research literacy and conduct, and well-developed programs to train CAM institution faculty in research are virtually non-existent. As part of a National Center for Complementary and Alternative Medicine (NCCAM) initiative to increase research capacity at CAM institutions, the New England School of Acupuncture (NESA), in collaboration with the Harvard Medical School (HMS) Osher Institute, was awarded a Developmental Center for Research on Complementary and Alternative Medicine (DCRC) grant. This article discusses a number of initiatives that we designed and implemented to train NESA students, faculty members, and alumni in the foundations of clinical research and to stimulate interest in both participating in research and receiving additional research training. Specific initiatives included a 30-hour faculty “Foundations of Research” course; a year-long course entitled, “How to Write a Publishable Case Report”; institution of a monthly research seminar series; revision of an already required student research course; and the addition of 2 new student-mentored independent research electives. We discuss successes and challenges encountered in developing and administering these initiatives and the overall impact they have had on research culture and productivity at NESA. (Altern Ther Health Med. 2008;14(2):52-58.)

Editor’s note: This article is a follow-up to an article that appeared in our Jan/Feb 2008 issue, “Increasing Research Capacity at the New England School of Acupuncture: Building Grants Management Infrastructure” (Altern Ther Health Med. 2008;14(1):56-64).
capacity at NESAs—namely, research education and training programs for faculty members, students, and alumni. We begin by reviewing the status of research training available at Oriental medicine (OM) institutions like NESA in the United States and then describe a number of interrelated initiatives aimed at improving research knowledge and research capacity within the NESA community. We discuss initiatives that have been successful, challenges we have encountered, and lessons we learned that might be relevant to other CAM institutions that wish to develop a research program. A more complete discussion of the scope of NESA's research program and the aims and structure of its DCRC program within which these educational initiatives were developed can be found elsewhere.4

RESEARCH TRAINING AT NESA AND OTHER ORIENTAL MEDICINE COLLEGES AND INSTITUTIONS

Even in OM schools with advanced master's and doctoral degree programs, training in research literacy and research conduct for students is very limited, as curricula generally focus on the development of practical clinical skills. The Accreditation Commission for Colleges of Acupuncture and Oriental Medicine (ACCAOM) does not have any formal requirements for research training. Some OM schools in the United States currently offer 1 basic course in research; however, the content of these courses varies considerably across institutions. Only a few offer advanced electives in research and/or provide students with opportunities for practical research experience or training. Well developed programs to train OM faculty in research are virtually nonexistent.

Like most other OM colleges, before the establishment of NESA's research program, NESA was primarily a “vocational,” clinically-focused program. An aim of both NESA's overall research program and the DCRC was to increase faculty, student, and alumni literacy, knowledge, and skills related to clinical research so that members of the NESA community could become effective clinical researchers. To address this aim within the DCRC, an education sub-committee was established that helped develop and oversee 5 initiatives related to faculty, student, and alumni training in research. The committee was composed of NESA's research director, HMS Osher Institute's director of education, NESA's student research coordinator, and faculty members representing all research-related courses. The 5 initiatives were (1) a new course for NESA faculty and alumni entitled, "Clinical Research Methods and Evaluation"; (2) a second new faculty and alumni course entitled, "How to Write a Publishable Case Report"; (3) initiation of a community-wide, monthly OM research seminar series; (4) curriculum revisions of an already existing and mandatory student research course; and (5) development of 2 new student electives in mentored research. Each initiative has involved both NESA and HMS faculty members. Table 1 summarizes these initiatives.

### Faculty Clinical Research Methods and Evaluation

This introductory course represents the first research-related training initiative created for NESA faculty and alumni. The aims of the course are to (1) introduce the fundamental principles and methods of clinical, epidemiological, and basic mechanistic science research design, conduct, analysis, and interpretation; (2) develop the skills and literacy required to locate, retrieve, and evaluate the published OM literature critically; and (3) understand the special issues related to the conduct of CAM or OM research. The course is taught in 3 discrete units over 3 weekends. The goal of the first unit, which covers the fundamentals, is to introduce participants to the scientific method and to specific types of scientific inquiry, focusing especially on the randomized controlled trial (RCT). The unit describes the rationale for the RCT and the methods used to conduct trials (especially acupuncture trials), including theory and hypothesis generation, blinding, randomization, statistical analysis, and procedures used to reduce bias. This unit concludes by introducing students to some of the challenges of conducting ecologically valid RCTs of acupuncture and the unique challenges related to acupuncture control interventions.

### Table 1: Summary of NESA DCRC Faculty and Student Research Training Initiatives*

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Target population</th>
<th>Hours; frequency offered</th>
<th>Key goals</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Research Methods and Evaluation</td>
<td>Faculty, alumni</td>
<td>30; annually</td>
<td>Fundamentals of research design; research literacy; key topics in OM research</td>
<td>Continuing education credits</td>
</tr>
<tr>
<td>How to Write a Publishable Case Report</td>
<td>Faculty</td>
<td>24; bi-annually</td>
<td>Contribution of case studies to evidence; greater familiarity with primary literature and writing skills</td>
<td>Continuing education credits</td>
</tr>
<tr>
<td>Research Seminar Series</td>
<td>Faculty, students, alumni, staff, public</td>
<td>1; monthly</td>
<td>Exposure to acupuncture researchers presenting results of recently completed or ongoing clinical or basic research</td>
<td>Continuing education credits</td>
</tr>
<tr>
<td>Foundations of Research</td>
<td>Students</td>
<td>30; annually</td>
<td>Fundamentals of research design; literacy; key topics in OM research</td>
<td>Required Course</td>
</tr>
<tr>
<td>Research Electives I &amp; II</td>
<td>Students</td>
<td>90 each; annually</td>
<td>Mentored independent research; clinical experience or secondary analysis of literature</td>
<td>Onsite or offsite</td>
</tr>
</tbody>
</table>

*NESA indicates New England School of Acupuncture; DCRC, Developmental Center for Research on Complementary and Alternative Medicine; OM, Oriental medicine.
The second unit introduces participants to (1) different methods for critically reviewing and evaluating research and (2) purported mechanisms of action (eg, neuroimaging studies, connective tissue signaling research). Participants take on mini-projects and learn how to do literature searches. Working in teams, they become familiar with databases, learn how to conduct a literature search on a specific OM topic, and then collectively work to evaluate a select group of published RCTs according to both established criteria (Jadad’s scale) and newer standards used to evaluate acupuncture (eg, STRICTA).  

In the final unit, participants present short literature reviews on topics of interest. This final unit also covers new innovative methods for studying OM (including qualitative research, development of valid OM measures). In this unit, participants also return to the question of what method should serve as the appropriate control for studies of acupuncture. At this point in the course, participants have reviewed and evaluated a wide range of studies including functional magnetic resonance imaging and basic science studies. They also have discussed studies that report to validate different methods for controlling for the non-specific effects of acupuncture. By returning to the issue of acupuncture controls that they initially considered in the first session, participants come to appreciate the growth they have experienced in their knowledge base and sophistication.

The course content is similar to that of an already existing and required student research course that is discussed later, although the format and some of the content is varied when taught to faculty and alumni. Both this and the student course were developed and are taught by 2 active OM researchers (Drs Conboy and Kerr) who hold faculty appointments at both NESA and HMS. A more detailed outline of the curricula for these courses is presented in Table 2.

Because NESA faculty members tend to have busy teaching and clinical schedules and because research is not always viewed as clinically relevant to OM practitioners, a number of strategies were developed to recruit faculty to this course. First, faculty members were surveyed to ascertain the most convenient timing and format for the course. The results of this survey indicated that conducting the course over 3 sequential weekends (30 contact hours in total) was most practical. Second, the research director sent a personal letter to all faculty members announcing and describing the course and highlighting how important and unique an opportunity this was for the OM community, NESA, and the faculty members’ personal professional development. This campaign was supplemented by announcements in faculty meetings and newsletters and personal phone calls. Finally, the course has been offered at no cost to active faculty members, and faculty members and participating alumni have been awarded continuing education (CE) credits. The course was also open to the larger community for a fee and was advertised as such through the NESA Continuing Education Program, which advertises nationally.

The course has now been offered twice and was well attended. The first time the course was offered, 8 of 70 faculty members attended. In the second offering, there were 13 participants (12 actively practicing alumni and 1 new faculty member). In both years, the program received excellent reviews. Representative qualitative evaluations of this course included the following comments: “this kind of course is something every acupuncturist needs to take”; “the creative exchange of ideas between the scientists and acupuncturists was fascinating”; “far more interesting

<table>
<thead>
<tr>
<th>Modules</th>
<th>Examples of topics and questions considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction to theory and research</td>
<td>What is science? What is research? What are special problems facing investigators studying OM?</td>
</tr>
<tr>
<td>Basics of designing a scientific study</td>
<td>What is a hypothesis? What is a causal relationship?</td>
</tr>
<tr>
<td>Finding and evaluating primary research</td>
<td>What tools are available to locate and retrieve OM research articles? What are the key issues to consider in</td>
</tr>
<tr>
<td>literature</td>
<td>critiquing a research study?</td>
</tr>
<tr>
<td>Research ethics</td>
<td>What is an institutional review board and what are its functions?</td>
</tr>
<tr>
<td>Basics of measurement and outcomes</td>
<td>How do you evaluate your measure? What do reliability and validity mean?</td>
</tr>
<tr>
<td>Sampling</td>
<td>When should you sample and why? What are your sampling options?</td>
</tr>
<tr>
<td>RCTs</td>
<td>What is random assignment? Why is it employed? History and prominence of the RCTs. Challenges RCTs pose to</td>
</tr>
<tr>
<td>Introduction to quantitative analysis</td>
<td>OM research.</td>
</tr>
<tr>
<td>Introduction to qualitative analysis</td>
<td>What is field research? Conducting field research: interviews, analysis of qualitative data.</td>
</tr>
<tr>
<td>Grant-writing skills; public presentations</td>
<td>Students work alone or in groups to formulate a research project, either a grant proposal or research paper in</td>
</tr>
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<td></td>
<td>grant-draft form. Projects are presented to the larger class.</td>
</tr>
</tbody>
</table>

*Format and emphases of some content vary between faculty/alumni vs student course (eg, grant not part of faculty offering).
†NESA indicates New England School of Acupuncture; RCT, randomized controlled trial; OM, Oriental medicine.
and enjoyable than I expected”; “reading clinical research in this group really improved my skills and confidence in critically evaluating primary literature on my own”; and “one of the best CE classes I’ve ever taken.” Quantitative evaluations of course content and delivery received an average score of 4.9 of a maximum score of 5.0. We plan to continue offering this course annually. It is now administered through NESA’s continuing education program and is open to alumni and other OM and CAM professionals.

"How to Write a Publishable Case Report or Case Series”

Based on the positive experiences with the first faculty/alu

TABLE 3 Curriculum Outline for Faculty/Alumni Course, “How to Write a Publishable Case Report”

<table>
<thead>
<tr>
<th>Modules</th>
<th>Examples of topics and questions considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Reports: Overview</td>
<td>What is a case report and what is it used for? What are the differences between observational and clinical investigations? What is the place of case reports in evidence-based research?</td>
</tr>
<tr>
<td>Types of Case Reports</td>
<td>What are the differences between retrospective and prospective reports? What are the differences between case reports and case series and cohort studies?</td>
</tr>
<tr>
<td>Identifying and Retrieving Peer-reviewed Research Literature</td>
<td>What is the process of conducting an electronic literature search? What are the basics skills needed to use PubMed, Medline, and related search engines? How does one retrieve full-text articles?</td>
</tr>
<tr>
<td>Critically Evaluating Primary Literature</td>
<td>How do we critically evaluate an already published case study? What are the key features to consider? What makes a case worthy of publishing?</td>
</tr>
<tr>
<td>IRBs*</td>
<td>What is the history and purpose of IRBs in protection of human subjects in research? What kinds of case studies require IRB approval? How does one complete an IRB protocol application?</td>
</tr>
<tr>
<td>Outcome Measures</td>
<td>Why are outcome measures important for case reports? What are the categories of outcome measures? How does one choose the most appropriate outcome measure(s)?</td>
</tr>
<tr>
<td>Writing</td>
<td>What is the structure/format of a case report or case series? What is the function of the background, results, and discussion sections?</td>
</tr>
<tr>
<td>Publishing a Case Report</td>
<td>Why is publishing case reports of potential value to both researchers and clinicians? How is authorship of papers determined? How does one determine the most appropriate journal for submission? How does one find out about the instructions/guidelines for authors regarding formatting and submission of manuscripts for review? How does one evaluate and respond to reviewers’ comments?</td>
</tr>
</tbody>
</table>

*IRB indicates institutional review board.

As with the first faculty course, a number of initiatives were undertaken to recruit faculty to this course. The course was initially designed to span a 9-month period, with one 2-hour meeting per month. Due to slower than expected progress in meeting our course goals, particularly with respect to facilitating faculty members in developing their cases, the course has been extended to a full year. The course was first offered in fall 2005; at the time this paper was written, it was more than 75% complete. Eleven faculty members have enrolled in the course; only 2 had participated in the Foundations of Research course. Group meetings have been lively and productive. To date 9 faculty members have identified cases to develop and submitted protocols for IRB approval or exemption. Example protocol titles include “Acupuncture regulates atrial fibrillation: a case report”; “A profile of users of Chinese herbal medicine at an inner-city Oriental medicine clinic”; and “Acupuncture for generalized anxiety disorder: a case series.” An evaluation for the course assessed at 7 months included the following comments: “This course has taught me that excellence as a practitioner is only part of my job the other part is contributing to the public discourse on acupuncture by publishing”; “My skills in the library were outdated.
This course helped bring me up-to-date”; “Very little of the research on acupuncture is helpful in my clinical work. Learning about observational studies in this course showed me a way for clinicians to help change that.” We will continue to offer this course to faculty and alumni every other year. Future offerings will be administered through NESA’s CE program.

Research Seminar Series
Taking advantage of the large quantity and diversity of research taking place in the greater Boston area, a monthly research seminar series was established to expose the NESA community to cutting-edge OM research and researchers. This initiative has been successful in many ways. First, we have had little difficulty attracting high-caliber speakers who are either located in the Boston area or willing to present during visits to the area. Since March 2004, we have hosted 22 speakers. Fourteen have presented work supported by NIH grants, and 13 are faculty members who are associated with HMS-affiliated institutions. Six NESA faculty members involved in research have also presented their work. A representative list of the topics addressed by seminar speakers is presented in Table 4. Most seminars, which generally take place during lunch, have been well attended, with an average of 20 to 25 participants consisting of approximately equal numbers of faculty members, students, and members of the general public. These monthly seminars have had a significant impact on NESA’s culture. They have exposed the NESA community to cutting-edge work, and researchers from other institutions have showcased their own faculty members as contributors to this research and fostered greater appreciation for the value of academic research to clinical practice and to the credibility of the OM profession as a whole. As of March 2006, faculty and alumni receive CE credit for attending research seminars. This seminar series will continue to meet on a monthly basis throughout the academic year.

Foundations of Research and Elective Courses for Students
Since 1998 all students at NESA have been required to participate in a 30-hour course introducing the basics of clinical and epidemiological research. Upon establishing our DCRC, the broad aims and content of this course were revised (Table 2). For students who complete this course and are interested in pursuing further research experience, a new pair of mentored research electives was developed in 2004. Students who enroll in these electives are partnered with a research mentor based either at NESA or in another Boston-area research institute. Projects can involve conducting literature reviews, serving as a research assistant in an ongoing study, or developing and/or conducting a small pilot study of their own, alone or with other students. Working with the mentor, each student is required to write an elective proposal with clearly defined learning objectives and final products. The proposals are then reviewed, and if deemed qualified, approved by NESA’s student research coordinator—a faculty member in charge of student research. Full academic credit for this elective requires a minimum of 90 hours of project-related activity. Students can take this elective up to 2 times for academic credit. These electives do not necessarily add additional credit hours to the program, as they are taken instead of other clinically-based electives. To date, 10 students have formally registered for this elective. Representative projects include an audit evaluating the quality of NESA’s student clinic medical records; a systematic literature review of clinical trials employing traditional Chinese medicine diagnoses as a design or outcome variable; a literature review of the different types of controls employed in RCTs evaluating acupuncture efficacy; and development of a tai chi research literature database.

Research Training Through Hands-on Participation in Clinical Trials
In addition to the initiatives described above, another important mechanism for research education and training has been the active engagement/participation of NESA faculty, students, and alumni in ongoing studies. For example, our DCRC supports 2 pilot clinical trials of acupuncture that have engaged faculty members and students in a variety of ways, including having them serve as project co-leaders (n=2); project coordinators and/or research assistants (n=5); and acupuncture protocol developers and providers (n=10). A third DCRC-supported methodological study is focused on evaluating the reliability of the OM diagnostic process and developing a validated diagnostic instrument. This study alone has engaged more than 50 acupuncturists (the majority of whom are NESA faculty or alumni) as expert consultants or diagnosticians. In addition to providing an opportunity for direct participation in a state-of-the-art NIH-funded clinical trial, each of these studies provides a substantive orientation session for acupuncturists during which the rationale and design of the study is described and discussed. Participation in these and other non-DCRC NESA trials continues to provide invaluable practical research experience that complements and informs the more didactic learning that takes place in courses and seminars.

DISCUSSION
Although many of the education and training initiatives described above are still in their early phases of implementation, there are a number of indications that they are positively impacting the general research knowledge/literacy of faculty members, students, and alumni within the NESA community and also providing a pool from which more interested and motivated individuals can be trained to become part- or full-time researchers.

First, our faculty, students, and alumni have become more interested and engaged in research. During the period of support for our DCRC, more than 75 faculty members and alumni have been involved in some aspect of an externally funded research study; some of these studies were not related to the DCRC. During this time, our faculty members have published more than 25 peer-reviewed articles related to CAM. A number of these are the first peer-reviewed papers to be published by certain faculty members. Additionally, more than 30 NESA students have
participated in some form of research through serving as research assistants or undertaking independent studies. Perhaps more significantly, to date, NESA has graduated at least 10 students who now include research as a significant component of their OM career (eg, project co-investigators, coordinators, research assistants, intervention providers); most were students during our period of DCRC support.

In addition to these tangible and practical accomplishments, the DCRC has been a significant catalyst in helping NESA achieve its more conceptual goal to transform from a primarily “vocational” institution to an academic institution. The training initiatives described above have provided a vehicle for faculty and staff development and a forum for collegial interactions. One of the most common responses we have received from faculty members who have participated in our research courses and seminars is that the opportunity to engage in scholarly discussion with

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<th>Institutional affiliation</th>
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<td>Vitaly Napadow, PhD, LicAc</td>
<td>What Can Functional MRI Tell Us About Acupuncture and the “Sea of Marrow” That We Don’t Already Know?</td>
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<td>Strengthening the Evidence Base for Acupuncture: Quality Assessment of Randomized Controlled Trials, 1997-2002</td>
<td>Oregon College of OM</td>
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<td>Acupuncture in the Treatment of Depression</td>
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<td>Weidong Liu, MB, LicAc</td>
<td>Acupuncture in the Treatment of Neutropenia</td>
<td>NESA</td>
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<td>Jongbae Park, PhD, LicAc</td>
<td>Evaluating the Effectiveness of Acupuncture: A Personal Experience</td>
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<td>Helene Langevin, MD, LicAc</td>
<td>Acupuncture: The Connective Tissue Connection</td>
<td>University of Vermont</td>
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<td>Julie Buring, ScD</td>
<td>Evaluating the Role of Vitamin E in the Prevention of Heart Disease: the Women’s Health Study</td>
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<tr>
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<td>Judith D. Schaechter, PhD</td>
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<td>Acupuncture in the Treatment of Post-menopausal Hot Flashes</td>
<td>NESA, HMS</td>
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<tr>
<td>Charles Shang, MD</td>
<td>Biology of Acupuncture: From Observation to Prediction</td>
<td>HMS</td>
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</tbody>
</table>

*NESA indicates New England School of Acupuncture; MRI, magnetic resonance imaging; HMS, Harvard Medical School; MGH, Massachusetts General Hospital; OM, Oriental medicine; MIT, Massachusetts Institute of Technology.

TABLE 4 Examples of Invited Speakers and Topics Addressed in the NESA Research Seminar Series*
their peers was the most enjoyable part of the experience. It is our expectation that over time, our training initiatives will not only continue to positively impact faculty knowledge and culture but will also positively impact how and what students are taught in didactic and practical classes. There is some indication that this is beginning to happen. For example, one faculty member who graduated from our basic research course has already begun to integrate practical evidence-based exercises into her OM pathology course and is beginning to explore how to expand such modules throughout the entire NESA curriculum.

The DCRC education and faculty development activities described above have also catalyzed and dovetailed with broader initiatives led by NESA’s governance and administration to further cultivate and promote scholarly activities. For example, during the DCRC program, NESA’s faculty ranking scheme was altered to more closely resemble that of an academic institution; participation in scholarly activities such as research and publishing now plays a more prominent position in faculty ranking and promotion criteria. Since beginning our research program at NESA, we have added 5 new faculty members with doctoral-level degrees—all are directly involved in research. Additionally, 6 newly formed half-time faculty positions now explicitly include up to 30% supported time for participation in research, writing, or other academic pursuits. The approval of 2 new research electives also reflects a commitment to foster more academic opportunities for students. The value of these programmatic and cultural shifts is supported by a survey conducted in 2005 among incoming NESA students that indicated that 41% of them were attracted to NESA because of its involvement in research. It is expected that over time, the presence of a stable, well-integrated research program will continue to catalyze NESA’s evolution toward a more academic, university-type environment.

The growing presence and impact that research training and our research program in general has had on the culture of NESA has not been without some resistance and questioning. One barrier we encountered to the more widespread integration of research at NESA is concern that scientific research and OM may not be compatible. Many faculty members and students at NESA were initially attracted to OM explicitly because it represents an alternative and more holistic philosophy and approach to health than scientific, evidence-based conventional medicine. For some, the current reductionist research paradigm is believed to be inadequate (too limiting) for studying complex, holistic, energy-based interventions such as acupuncture. According to this perspective, current approaches to research will inevitably result in biased conclusions that are unlikely to be of benefit to the OM community. This perspective is not unique to NESA and has been well articulated in a number of recent debates regarding the benefits and limitations of the current evidence-based models for evaluating CAM practices.2,3,5 Acknowledging, honoring, and sometimes sharing this concern, NESA’s research department has been careful to emphasize that one of the motivations for our program is to engage our faculty in research so as to challenge this paradigm and help develop alternative research models and methodologies. Indeed, the majority of studies initiated at NESA have included unique design components (eg, individualized treatments, minimally invasive controls) that honor and integrate clinically relevant practices. As more of our community learns about research and participates in it first-hand, this barrier to the more widespread integration of research into our community is declining.

A primary motivation underlying NCCAM’s DCRC program is the belief that sound CAM research requires the meaningful participation of CAM practitioners in all aspects of research—from study conception and identification of specific hypotheses to development of treatment interventions, choosing outcomes measures, and interpreting results. Without significant training to improve research competency, however, the participation of CAM institutions in research is highly unlikely. The initiatives described in this article represent our attempt to provide education and training to improve basic research knowledge and competency among NESA faculty members, students, and alumni. Our curriculum and initiatives can be modified to suit other CAM institutions wishing to develop a research program. Research education/training is an important element in NESA’s strategy for building a sustainable, productive OM research program. Other elements of this strategy include initiatives at NESA to build grants management infrastructure, to establish an independent institutional review board to oversee the ethical conduct of trials, to develop an OM research library, and to establish a fund-raising development program to help find alternative sources of income to supplement federal grant support for research.4

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In The Log from the Sea of Cortez, John Steinbeck relates how his friend Ed Ricketts, after the destruction by fire of his Cannery Row laboratory, testified at a trial in the Superior Court in Salinas. His company, Pacific Biological Laboratories, Inc, was one of the plaintiffs in a suit against the electric company, unsuccessfully alleging that the fire was caused by error or negligence by the company. “Now you take the case of this fire,” he went on. “Both sides wanted to win, and neither had any interest in, indeed both sides seem to have a kind of abhorrence for, the truth.”

In this article we examine an exemplar (dietary supplements) of the clash between science and law and the dangers inherent in judges wandering in the murky field of scientific controversy and using it as the basis of a judgment.

**THE CASE**

In Commerce Commission v Zenith Corporation Limited (Auckland, New Zealand), the defendant ultimately faced 23 pairs of alternative charges, all concerning representations in promotional materials for “Body Enhancer” or its successor, “Neo Nutrients Body Enhancer.” Twenty-three charges alleged representations liable to mislead the public as to the suitability for a purpose of goods, in terms of sections 40(1) and 10 New Zealand Fair Trading Act 1986 (FTA); 23 alternative charges alleged false or misleading representations as to the benefits of goods, in terms of sections 40(1) and 13 FTA. Two of the original informations (ie, legal filings) were withdrawn. The defendant also faced 3 charges relating to representations made on labels of “Neo Nutrients Body Enhancer,” which are not relevant to this article. All of the alleged offenses pre-dated the 2003 amendments to the FTA. Section 13 FTA was amended in 2000 and took effect November 15, 2000. By that date, the events that were the subject of some of the charges outlined above had already occurred, but others giving rise to the remaining charges had not. The effect of the amendment was to replace “false” in the section heading with “false or misleading” and to replace “falsely represent” as the opening words of each of paragraphs 13(a)-(f) with “make a false or misleading representation.” The charges alleging a contravention of section 13(e) reflected that amendment. The charges were based on representations in pamphlets and radio and magazine advertisements and on a website saying that the product “will assist with” a variety of conditions, including weight loss; liver detoxification; preventing the effects of body collagen depletion; healing of cartilage and strengthening of joints, tendons, and heart muscles; and others.

Witnesses called by both the prosecution and the defense gave expert evidence. Judge Moore was critical of some evidence given by expert witnesses called by the defendant. He described Professor Vitetta, for example, as a witness “whose approach seemed founded on a sense that his task was to produce additional or contradictory evidence rather than to form an overview which took into account all relevant material.” Dr Cortizo was said to be “quick to find opportunities to allege bias on the part of witnesses for the informant but, despite his skills at diversionary tactics, that approach, or rather the justification for it, did not survive cross-examination.” Generally, expert witnesses called by the Commission found favor with Judge Moore. He found that Professor Swinburn “adopted apt strategies and limitations, and that the work and study which lay behind his evidence was carried out skilfully, painstakingly, logically and with integrity.” Professor Mann was said, like Professor Swinburn, to be “calm, measured, analytical and detached.” Dr Barling “presented as a very relaxed man, entirely comfortable with who he was and where he was at.”

Before convicting the defendant on 26 charges, Judge Moore summarized the expert evidence. When asked, “How simple...
would it be to conduct a randomised control [sic] trial of a weight loss product such as Body Enhancer?” Professor Swinburn replied, “It would be extremely simple actually.” In his evidence, Professor Mann stated that the randomized controlled trial (RCT) is “an integral part of evidence based medicine and should wherever possible inform medical opinion and practice” and that “several RCTs reviewed by a panel of appropriately experienced professionals or reanalysed statistically in a meta-analysis is regarded as the highest level of evidence.”

He noted that RCTs on the effect of vitamin E on humans had reversed earlier research on animals that had indicated that vitamin E could favorably improve several risk factors for coronary heart disease and stated that “there is no reason evidence [sic] why the reported ingredients of Body Enhancer or indeed the product itself could not or should not be assessed using strict RCT procedures.” He saw such a trial as “conceptually simple, it would probably be moderately costly.”

Professor Mann went on to note that even after a compound has been tested in several RCTs, several factors, such as form of delivery, route of delivery, matrix, form of the compound, purity of the compound, quantity/dose, and physiological state of the recipient should be considered when assessing claims about efficacy. Although Judge Moore emphasized with respect to all of the charges that “a conviction can be entered only if the informant proves the guilt of the defendant beyond reasonable doubt” and that “there is no obligation on the defendant to prove its innocence or to prove anything else,” he included the following in his judgment:

One of the noteworthy features of the evidence before the Court is that, other than the references to dexfenfluramine and orlistat (Zenical [sic]) it does not include even a reference to any properly conducted clinical studies as to the efficacy of extensively marketed weight loss products, whether patented or not. Yet on the evidence before this Court, sales of Colorado long ago exceeded $US200 million. If success had been achieved in the commercial exploitation of any one of the many patents before the Court, it would be surprising if that had not given rise to properly conducted double blind clinical trials to provide a foundation, not only for the advertising of therapeutic claims, but the re-launch of the product as a recognized medicine, able to be prescribed by doctors. There is, of course, nothing of the sort.

He noted that it was only when faced with prosecution that Zenith took any steps to obtain a controlled trial of the product, and had then contacted a person he described as an “entrepreneurial doctor” rather than a reputable organization with the skills necessary for the proper design, conduct, and analysis of such a trial. Noting that there is more than 1 accepted scale of classification of clinical studies and similar research, he nevertheless saw “double blind randomised controlled trials in which neither the study participants nor those directly involved in the conduct of the trial know whether any particular participant is receiving a placebo or the substance being tested” as the “gold standard.”

THE LAW AND RANDOMIZED CONTROLLED TRIALS

Was the judge on good grounds adopting such a stance? To answer this we need to examine the nature of science itself and in particular the RCT. Although the Cochrane Collaboration lists more than 4000 CAM-related RCTs in its database, many manufacturers and distributors of complementary and alternative treatments cannot afford to conduct such a trial. RCTs are generally conducted by manufacturers of conventional medicines, most often to satisfy the US Food and Drug Administration, which decides whether a manufacturer has provided “substantial evidence” from “adequate and well-controlled investigations” that a drug is effective for its intended use. This decision has usually been based on more than 1 RCT.

This procedure has not escaped criticism. Research can be falsified but because of the possible criminal and civil penalties, harm to reputation, and a possible continuing absence of trust by the regulating authorities, such falsification is generally avoided, if only because “there may be ways short of fraud to control the outcome of research.” Those ways include biases in the design of a research study and in the reporting of such a study, either or both of which may be related to the so-called “funding effect”—the name for the fact that “strong and consistent evidence shows that industry sponsored research draws pro-industry conclusions.” In addition to these objections, there are other, more philosophical objections to the primacy of the RCT.

EVIDENCE-BASED PRACTICE: RANDOMIZED CONTROLLED TRIALS AND THEIR LIMITATIONS

In opting for the RCT as the gold standard, Judge Moore wandered into the field of evidence-based practice, at the heart of which is the RCT. The definition formulated for evidence-based medicine is that it is “the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.”

The dominant focus of evidence-based practice has been the RCT. However, it is not the single RCT that is the gold standard; rather it is the systematic review of trials that is the most significant, particularly those that result in a meta-analysis. In fact, the results of even a double-blinded trial can be misleading, particularly if the number of subjects is insufficient to power the study (ie, give it statistical legitimacy). Meta-analysis overcomes that problem by combining studies that are homogeneous so that the subject pool is larger.

Although other forms of study design may be included in a systematic literature review (non-random trials, cohort studies, and simple pre/post case series) the RCT is given most weight since it is the design that most clearly establishes efficacy. Unfortunately, such studies generally test a therapy under ideal conditions and often with homogeneous populations to ensure
comparability of the groups when comparing outcomes. But evidence-based practice ultimately requires therapies that can be applied in normal practice, that is, effectiveness studies. Just as a therapy without any efficacy will not be effective, a therapy that demonstrates efficacy in a study may not be effective when applied to heterogeneous populations under normal practice conditions. Furthermore, therapies with equal or comparable efficacy may differ considerably in terms of effectiveness.

In contrast, however, RCTs test therapies under ideal conditions and therefore do not often help with determining effectiveness in everyday practice as opposed to efficacy in a controlled, and usually perfect, setting. There are some very strict ethical limitations to conducting clinical trials that prevent certain populations from participating. If there is a very high risk but low benefit for a sub-group of patients, this might mitigate against them being included (such as patients with high co-morbidities). Conversely, some low-risk patients may not be included because too large a number would need to be enrolled to make the study feasible. The end result, therefore, is that clinically it is not possible to know if the therapy can be applied to groups that were not included in the trial.

Although providers do treat populations, they treat them one at a time. RCTs seldom contain the “soft data” about individual variations, particularly in response to therapy. The type of clinical detail essential for a provider to decide whether a given patient is a candidate for a drug, procedure, or therapy is seldom provided in an RCT. RCTs provide the results of average patients and even then it is an average of those who meet the inclusion criteria. This problem can be solved through observational studies.

There is a dilemma, however, about the role of observational studies. On the one hand, they may seem more clinically relevant and include the populations and sub-populations of interest to the health provider, but on the other they do not provide the type of definitive evidence that might persuade the provider to recommend the procedure to the patient. Despite this ambivalence, observational studies continue to be widely published. Ray, in a 2-month survey in 1998 of 3 leading medical journals, found that observational studies comprised 68% to 87% of their featured articles and communications, and only 32%, 13%, and 26% of their publications were RCTs. He notes that although we do not know how observational studies impact practice or policy, given their propensity to publish them, these journals must feel that observational studies are important to their readers.

One solution to the dilemma in evidence-based practice has been to create a hierarchy of evidence. A standard hierarchy is the following (from the highest to the lowest): evidence provided by at least 1 appropriately designed RCT; evidence provided by a controlled trial that is not randomized; evidence provided by a well-designed cohort or case-control study; evidence provided by a multiple time series, descriptive studies, case reports, and opinions of experts or respected authorities.

There is an expanding body of literature on studies examining RCTs and observational studies for the same disease and intervention. As Ioannidis et al note, earlier studies concluded that nonrandomized studies overestimated treatment benefits. More recently, the studies show that both randomized and nonrandomized studies yield very similar results. Their own study found a very good correlation between the 2 but that the nonrandomized studies did show larger treatment effects. Interestingly, they found that heterogeneity was frequent between studies in both groups. Benson and Hartz found little evidence of a difference in the treatment effects between RCTs and observational studies when the comparison was made for the same treatment.

Concato, Shah, and Horwitz found in their study that in the 5 topics they examined where there were bodies of both RCTs and observation studies, the results of well-designed observation studies did not systematically exaggerate the magnitude of the effects of treatment compared to the RCTs for the same topic. They concluded that their results challenge the hierarchy of evidence being used in clinical research (and systematic reviews). Those studies with either a cohort or case control design did not overestimate the outcomes and the results of the RCTs and these studies were very similar. In fact, the observational studies have less variability in point estimates than did the RCTs. This also meant their results were less heterogeneous.

Discrepancies in RCTs and between RCTs and meta-analyses have been noted previously. This makes using a single RCT as the gold standard for care a questionable approach. As Concato, Shah, and Horwitz note, because of the inclusion and exclusion criterion used in RCTs, an observational study is more likely to include a broader representation of the population. They also note that earlier studies comparing observation studies and RCTs had included all types of observation studies in the comparison. If, however, the comparison is made with cohort and case control studies, the superiority of RCTs is not so clear. Of course, such a conclusion raises the question of whether there is a hierarchy of observational evidence. Stroup et al have put forward a proposal for improving the reporting of meta-analyses of observational studies in an attempt to answer the question of the quality of observation studies.

According to LeLorier et al, the recent research has begun to assert that quality observation studies are no more misleading than RCTs. The popular belief that only RCTs produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigations, and the education of healthcare professionals.

MEDECINE AND EVIDENCED-BASED PRACTICE

There is considerable debate about how much of clinical practice is evidenced-based. The initial estimates by the Office of Technology Assessment in 1978 and 1983 were that only about 10% to 20% of medicine could claim to be evidenced-based. As noted by Imrie and Ramey, this figure was simply an estimate. They further note that other commentators have given figures as low as 15% for practices based on any evidence. The problem of establishing any figure is you first need to define what will constitute the evidence. How you do that has a great impact on the result. If, for example, you demand only 1 good single RCT,
the figure will be much higher than if you required repeated RCTs. The use of a single RCT, no matter how good the study, does pose methodological problems. Single studies can be contradicted by later studies. To overcome the problem of a single study, studies are pooled if they are homogeneous enough to permit a meta-analysis. This also greatly increases the sample sizes on which analyses can be done. Examples of misleading meta-analysis have been documented in the literature. Furthermore, studies with negative results are less likely to be published. This has a tremendous impact on the “evidence.”

THE JUDGE AND THE SCIENCE

When a judge opts to accept the opinion of some scientific experts, he is in fact opting for the lowest ranked of all scientific knowledge in evidence-based practice. He is also supporting a scientific paradigm over others—in this case, evidence-based practice—and elevating 1 form of research design, the RCT, over all other forms. The problem with all this is there is good evidence that expert opinion is shaky at best and frequently downright wrong; there is an increasing body of research that questions whether the RCT is the gold standard the experts claim it to be. There is considerable evidence to suggest that medicine itself (or at least about 80% of it) could not meet the standard of evidence supported by RCTs and, last but not least, there is no evidence that evidence-based practice, where it does exist, results in better patient outcomes. In the face of this, how has the law dealt with expert opinion?

EXPERT SCIENTIFIC EVIDENCE

In common law, the general rule is that witnesses cannot offer opinion as evidence; one exception to that rule is that sufficiently qualified expert witnesses may give opinion evidence on matters within their area of expertise. That exception is in turn circumscribed by a series of subsidiary rules: the “common knowledge” rule, that such an expert cannot give evidence on a matter within the knowledge of the finder of fact; the “ultimate issue” rule, that such an opinion is inadmissible if it is an issue the finder of fact must determine; the “factual basis” rule, that the facts upon which the opinion of the expert is based must be proved by admissible evidence. There is considerable consensus internationally about the circumstances in which such evidence, particularly when it includes novel or controversial ingredients, can be introduced and considered in court. In R v Calder, introducing the topic of expert evidence of new scientific techniques or theories by quoting an Australian text that stated that “the issue of how to deal with areas that have not yet fully emerged from their developmental stages remains unsolved,” Judge Tipping examined authorities from England, Canada, Australia, and the United States. In Canada, in R v Johnstone, 14 points were seen as relevant to whether scientific evidence, if challenged, should be admitted or excluded; in R v Melarangi, 9 points, some of which were the same as or similar to those in Johnstone were deemed relevant. In Australia, in R v Lucas, Judge Hampel urged caution with respect to the introduction of challenged scientific evidence, referring to United States v Baller, in which it was noted that “because of its apparent objectivity, an opinion which claims a scientific basis is apt to carry undue weight with the trier of fact.” In the United States, the leading authority for many years had been Frye v United States, in which “general acceptance” of a scientific technique or theory was required.

That test had been the subject of considerable criticism, and the Supreme Court of the United States revisited the topic in light of the Federal Rules of Evidence in Daubert v Merill Dow Pharmaceuticals, in which it was decided that the “general acceptance” test in Frye was not a necessary pre-condition to admissibility. Among the factors the court recognized as relevant to whether expert scientific testimony should be considered was general acceptance, but other factors, such as peer review and publication, whether the theory or technique can be or had been tested, and potential or known rate of error, were also regarded as relevant to the question. The court saw the judge as playing a “gate keeping” role and believed that vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof were appropriate methods to attack shaky but admissible evidence.

Judge Tipping also received assistance from a New Zealand Law Commission discussion paper that—although recommending that scientific evidence should be assessed for reliability, including the reliability of the underlying theory and the reliability of the procedures and techniques used in a particular case—nevertheless contended that a theory need not be accepted by all or even most scientists in an area to be admissible, and that theories that were new or represented the views of a minority could be reliable and helpful. The discussion paper contended that procedures ought to conform to acceptable scientific standards, but that an opinion need not be conclusive in order to be admitted into evidence. In Calder, Judge Tipping ultimately decided that, to be admitted, such expert evidence should be relevant, helpful, and more probative than prejudicial; relevant, as in tending to show that a fact in issue is more or less likely; helpful, as in passing a “minimum threshold of reliability” test in that the proponent of the evidence demonstrates that it has sufficient claim to reliability to be admitted. Once the threshold has been crossed, the weight of the evidence and its probative force can be tested in cross-examination and counter evidence. Judge Tipping acknowledged that the “sufficient claim to reliability” test could be too general to be of much assistance, but saw flexibility as a desirable ingredient; the points set out in the Canadian cases Johnstone and Melarangi could be useful in deciding whether the threshold had been crossed. Whether the judge, as gatekeeper, opened the door or kept it shut in any individual case would depend on a wide variety of subsidiary issues.

CONCLUSION

Imagine that a corporation, instead of selling a weight-loss product, sold “retroactive prayer” and claimed that such prayer, offered from 4 to 10 years after an event, can affect outcomes. A randomized, controlled, double-blind, parallel group study
including 3393 patients considered the hypothesis that such retroactive prayer affects outcomes. The study concluded that, although mortality was similar in both groups, length of stay in hospital and duration of fever were shorter with such prayer.

Although there may be all kinds of other evidence, should that RCT evidence be conclusive were the corporation to be charged with a contravention of the Fair Trading Act 1986, or should the judge consider all of the evidence tendered? In deciding what evidence should be considered, it is fitting to conclude with another quotation from John Steinbeck, this time referring to one of Ed Ricketts’ fictional alter egos, “Doc,” in the novel Sweet Thursday, in which the local inhabitants decide to bid Doc farewell with a gift, knowing that he wants a new microscope for his laboratory.

Doc looked at the gift—a telescope strong enough to bring the moon to his lap. His mouth fell open. Then he smothered the laughter that rose in him.

“Like it?” said Mack.

“It’s beautiful.”

“Biggest one in the whole goddam catalogue,” said Mack.

Doc’s voice was choked.

“Thanks,” he said. “After all, I guess it doesn’t matter whether you look down or up—as long as you look.”

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focusing my attention on reading and schoolwork. I had great
difficulties in going through school. Because of that, I always had
the feeling something was wrong with me.

I was very tuned in. I could read people very well, but to
concentrate on a 2-dimensional task like looking at a book all
day was hard for me. I would start reading, and I’d feel very dis-
tracted or I would fall asleep. However, I had excellent eyesight.
Whenever my parents took me to the eye doctor, the doctor
would say, “His eyes are perfect.” No one ever put it together that
the difficulties that I was having in the classroom were in any
way related to my vision because vision was defined as eyesight,
and I had 20/20.

When I got out of high school and I entered college, about 10
days into the first semester the teacher gave us a pop quiz. I was
sitting in the back of the class because my eyesight had always
been excellent. In the middle of the test, I looked up at the black-
board, and the blackboard all of a sudden was fuzzy. And it stayed
fuzzy. I got very frightened; I didn’t know what was wrong. I fi n-
ished the test and then went to the eye doctor at the infi rmary.
Dr Liberman examined me and said, “Oh, you’re near-
sighted.” He didn’t tell me that my near-sightedness was just a
minute amount, and he never mentioned that I had had a spasm
in my accommodative or focusing system from doing so much
close work, which is, of course, what happens when you’re in col-
lege. He gave me glasses. I was just grateful I didn’t have some
pathology. So I started wearing glasses, and I could see the black-
board, but I still couldn’t read for longer than I’d been able to
before. In fact, reading became ever more uncomfortable.

Every 6 months or so, I would notice that I couldn’t see the
blackboard anymore, so I had to keep getting stronger and stron-
ger glasses. But nothing was changing in terms of my ability to
read and learn with greater ease. When I got into optometry
school, the reading demand increased significantly, and I was
barely getting by between working to pay my way through school
and having a full school load—optometry school is basically the
same pre-med as you get in a medical school. It’s very intense. The
first 2 years, I was so close to not getting by that I actually thought
they would not allow me to go into my third year. But they did.

When I entered my third year, which is when you start your
clinical training, they sent me down to the clinic, and they asked
one of the fourth-year doctors to examine me. They gave me a
sight, and that just because we vision is much more than eye-experience with the fact that I went from a 2.0 average to ending up in the top 10% of my class. I had a revelation. Something ed crying because my whole life, I comprehended in my life. That was my first profound experience with the fact that vision is much more than eyesight, and that just because we have 2 eyes open doesn’t mean that they’re both being used. You have 2 legs, but if you had use of only 1 of them, it would create a huge imbalance in your life. The same is true with your vision. If both eyes are not working together efficiently, it will affect your comfort and performance in a very significant way.

Additionally, if one’s vision is functioning excellently, his response to life will be perfectly timed, so if he’s playing baseball, the bat will be swung at the right moment, will hit the ball on the sweet spot and even if he doesn’t hit the ball hard, it’ll go a great distance. That’s great vision. So vision is not so much what you see, it’s what you do with what you see. It’s your response to life. That first experience, which happened in 1971, changed my life.

ATHM: What was your next step in getting to where you are today?

Dr Liberman: In my first several years of practicing optometry, I was very involved in working with young children and teenagers who had difficulties with learning because that was something that I knew by heart—that was my own story. I worked with thousands of kids. And in late 1975, the thought came to me: “I wonder if there’s anything that I can do that could in some way improve my eyesight.” Because when I went to school, I wasn’t taught that vision could affect everything; it was just an optical system, a camera inside the head. We were taught that eyes got worse because they were too long or too short or oddly shaped.

The idea that vision could be improved was never discussed. One of the first things that is taught in medical school is that the body is always seeking homeostasis, always seeking balance. We know health means balance. You could say that the heartbeat of life, of the universe, of the human body is a continua! movement toward equilibrium. I call it homeodynamics. It’s not really homeostasis; it’s just a continual movement, a search for balance.

This is probably why in science we say, “The only constant is change.” That change is the continual adjustment of the inside of the body to the environment. We know the body has the ability to self-heal, but for some reason or other, this is an unknown concept in the area of vision. Vision specialists know that very few people enter this world needing glasses or seeing poorly—probably less than 1%. Yet by the end of fifth grade, more than 80% of kids have measurable vision difficulties.

In many places where education is stressed, like Israel, Asia, and the United States, by the time kids are 16 or 17, well over 80% are near-sighted. The biggest health epidemic in the world right now is deteriorating eyesight, and yet all we do is give glasses or contacts. If you look at the records of any vision specialist in the world, you’ll notice that the moment a patient begins to wear glasses, his eyes continue to deteriorate. What I’ve always said is, if the problem gets worse, the solution can’t possibly be the solution.

And yet we’re not looking for the causative factor. We’re looking at using glasses or contacts or doing surgical intervention like LASIK as a way of neutralizing the problem, but we’re still not looking for the cause, and we’re still not broadening our idea of what vision is beyond the concept of eyesight. So in 1976, I started doing vision training on myself a few minutes a day and rather than continually increasing the prescription of my glasses, which is what my history for 10 years had been, I began reducing my prescription very subtly every 6 to 8 weeks, gradually allowing myself to adjust to a weaker prescription as my vision skills improved.

I also spent time without my glasses on, just to notice how it felt internally when I wasn’t wearing them. I wasn’t primarily concerned with whether I could see or couldn’t see, but rather how I felt emotionally. I noticed that I started feeling out of control and edgy without my glasses on and noticed that wearing the
Conversations: Jacob Liberman, OD, PhD

Why people say “I see” to indicate that they understand something. But to say something is in focus is to say it is clear. That’s a mantra. Focus on the third eye. Focus on something.

Even though the eyes are closed, they say, “Focus on a point.” This is also why most meditative practices have you focus on something.

The eyes are required for us to both suppress external noise and quiet our mind. In other words, aiming and focusing the eyes must converge upon that which is of interest.

Given your explanation of how big the definition of vision is, what is creating this epidemic of young people not being able to see clearly?

Dr Liberman: I’ll tell you exactly what it is. You live in Boulder, Colorado, a place where there’s a lot of expanse, a lot of space. When people step outside, most will breathe a sigh of relief because their eyes can escape all the way out to infinity. You know how do you know they’re paying attention to you? You know because their eyes can escape all the way out to infinity. You know because you’re paying attention to you? You know because they’re looking at you. In order to attend, to be present, the eyes must converge upon that which is of interest.

When the eyes aim or converge, they simultaneously focus. This process is inseparably connected with our ability to selectively attend and be present. In other words, aiming and focusing the eyes is required for us to both suppress external noise and quiet the mind. This is extremely important because being present and attentive is the most fundamental function involved in learning.

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This is also why most meditative practices have you focus on something. Even though the eyes are closed, they say, “Focus on a mantra. Focus on the third eye. Focus on something.”

When we think of the word focus, we think of an optical system. But to say something is in focus is to say it is clear. That’s why people say “I see” to indicate that they understand something. Seeing is inseparably connected with understanding. Aiming lays the foundation for presence and effortless attention, while focusing provides a sense of clarity and knowing.

Next comes tracking, which occurs at the same time as aiming and focusing. We say the only constant is change. So as things in the environment enter our field of awareness, the eyes are automatically moved toward them. It’s an effortless process because light and the eye are married. When light strikes the eye, the eye automatically moves toward it in the same way as a flower turns its face toward the sun. Tracking is the process of continually moving the eyes from one moment to the next as things in the environment call our attention.

So the eyes simultaneously aim, focus, track, and work together as a team. The teaming aspect of vision is very important because having 2 eyes gives us the ability to have stereoscopic or 3-dimensional vision. Dr Arnold Gesell, who at one time was the leading child-development expert in the world and who founded the Gesell Institute of Child Development at Yale, said that stereoscopic vision was the crown jewel of organic evolution. He said it was the most highly developed aspect of our neurological system.

Having 2 eyes not only gives us the ability to see depth, it also allows us to determine what’s foreground and what’s background, what’s most important and what’s less important at that moment. It lets us know where we are in space in relation to other things. Good eyesight is the ability, for instance, of a baseball player to see the pitcher clearly.

Good vision is the ability of that player to track the baseball at 95 or 100 miles per hour from the pitcher’s hand to the plate and be so integrated that his arms and body move at the exact moment necessary for the bat to hit the ball.

In the classroom, that level of vision provides a child the ability to effortlessly attend, allows the eyes to move smoothly across a line of print, so that reading and comprehension and attention become something that’s fun and easy. If a child is having any difficulty with these functions, learning becomes very difficult.

ATHM: Can you explain those functions in detail?

Dr Liberman: These 4 functions—aiming, focusing, tracking, and teaming—occur simultaneously and are inseparably connected to one’s consciousness. To give you an example, when you are speaking with someone and they’re paying attention to you, how do you know they’re paying attention to you? You know because they’re looking at you. In order to attend, to be present, the eyes must converge upon that which is of interest.

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how sometimes it’s a little more difficult to breathe deeply when you enter a small space such as an elevator? Well, we have 2 eyes in order to be able to see all the way out to infinity. However, if your visual space is confined, your body begins to show signs of stress. If you, for instance, put an animal in a visually confining environment, so that its eyes can look only as far away as 18 or 20 inches, that animal will become myopic. A high percentage of sailors that are in a submarine for a month or 6 weeks are near-sighted when they come out. Their near-sightedness may reverse, but visual confinement creates a constriction in vision.

Most of the epidemic of near-sightedness that we have today is because the demand on the eyes is for reading and learning. Most people spend a good part of their day either looking at a book 16 to 20 inches away or, even more commonly today, looking at a computer monitor. Many school children sit in windowless classrooms. Many people work in cubicles or in offices without windows.

The major problem is that our eyes are very often confined to a close distance, so they adjust to that distance because that is what society says is important for us to succeed. If our neurological system were designed for a 2-dimensional world, we would only require 1 eye in the center of our head. The reason we have 2 eyes is to give us 3-dimensionality. In other words, our entire neurophysiology is designed for a 3-dimensional world. When you read or work on a computer, you are restricted to 2 dimensions.

If you take a system that is designed for 3-dimensionality and primarily use it for 2-dimensional tasks, it creates stress. Studies that were done many years ago found that when children read a book, their pulse rate, respiration rate, etc—all the markers of stress—significantly increase. If you go into cultures around the world where people don’t go to school and don’t do a lot of reading, you see that near-sightedness is unheard of. Look at Eskimos, for instance: before Alaska institutionalized education, myopia was unheard of. However, as soon as Eskimos were required to go to school and read, there was a significant onset of myopia.

So the epidemic of deteriorating eyesight is caused primarily by the stress created by visual confinement. And the major source of visual confinement responsible for that stress is the cultural demand to sit and look at a book or a computer all day.

ATHM: What do you see as the remedy?

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Conversations: Jacob Liberman, OD, PhD

Dr Liberman: There are 3 remedies that I immediately see. First we need to redefine what it means to see. People need to become aware that vision is much more than just eyesight.

Next, I see 2 very practical remedies. In 1928, a group of visionary optometrists developed the science of functional optometry and vision training. They realized that vision is seamlessly connected with behavior and performance. And since vision affects every human function, they developed a behavioral science called behavioral optometry.

Today there are thousands of doctors who practice this type of care, and one of the major things they do, aside from vision training, is to prescribe stress-reducing glasses for kids to use in school for learning. These are not glasses that are prescribed because of poor eyesight. These are glasses that magnify very slightly and have a measurable stress-reducing effect. They function like a wedge. Let’s say you’re cutting a tree down and want the tree to move in a certain direction. Strategically placing a wedge of wood on one side helps the tree to fall in the desired direction. When we want the vision system to begin to normalize or move in a direction opposite of the way it’s moving, we frequently use what we call a wedge prescription. It’s a very small-powered magnifying lens that reduces visual stress and is used primarily for classroom work and reading. That by itself is a wonderful preventive tool. It’s a practical application that very often prevents the onset of myopia.

The most important recommendation is vision training. Consider the value of doing something like yoga, Pilates, or gyrotomics, some sort of exercise that maintains the body’s flexibility. If we began doing yoga as children, a little bit each day, not as an exercise but as just a part of our life, as we got older a lot of that flexibility would be maintained. The difference between youth and older age often is a loss of flexibility. If flexibility can be maintained in the body, then I think that it has a direct effect on not only our physical comfort but on our longevity and our well-being. The same is true with vision.

Another very effective tool is a little bookmark that I developed in 1976. It has a stop sign on top and says, “Stop. Look up. Look away. Breathe. Put me 2 pages ahead.” So that every time you get to that bookmark, you take a little break, just enough time to look up, look away, let the eyes escape, and relax the focusing system. If we merely gave each child in school one of these bookmarks, that in itself would make a very significant change in terms of the onset and progression of myopia.

If we just did a few simple vision-training exercises each day, along with using stress-reducing glasses for close work, I believe we would probably prevent most myopia. Beyond the prevention of vision deterioration, this approach would also optimize and expand our ability to see and learn.

We would attend better with less effort. We could read longer and more comfortably. Learning would be easier, sports performance would soar, and working at the computer would be more comfortable.

ATHM: How do you envision making these vision-training practices more widespread?

Dr Liberman: For years my dream has been to bring this awareness to the public. If I share these suggestions and skills with athletes, for instance, it significantly improves their game. Whether it’s baseball, golf, or tennis, athletes know that the key to peak performance, aside from physical conditioning, is their vision. And the same is true in the classroom. Our eyes guide everything we do.

We are now introducing this work to school systems, sports teams, computer users, pilots, and police recruit training programs. It’s a whole new paradigm, and the timing couldn’t be any better. It’s not only because we’re losing our eyesight as a species, but also one of the biggest epidemics today is attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD). Millions of children and adults are being medicated because they have great difficulty attending comfortably. I cannot tell you the huge difference someone can experience in their ability to attend, read, and learn by doing some very simple vision exercises.

To make that available to people, I developed a clinically proven device that can significantly improve those skills. And it’s...
backed up by peer-reviewed published research. What’s really interesting is that someone can spend less than 10 minutes a day doing these exercises and experience very broad effects—everything from improving visual attention and reading efficiency and comprehension to how comfortably they work at the computer and play their favorite sport.

Vision training has far-reaching effects, and very soon this information will permeate every area of life because as someone once said, “Next to life itself, God’s most precious gift is sight.” When we think about vision, what it means to see, it’s not just an optical process. Our vision is deeply rooted in our humanity.

A large part of my last 35 years of work has dealt with the effect of light on the mind, body, and spirit. Now I’m focusing on light, vision, consciousness, and performance and how all these things are connected. What I’ve discovered is that they are inseparable. Changing one’s vision can truly change one’s life.

One of the most powerful movements today is a drive toward personal growth and development. We read self-help books in an attempt to see and understand our lives more clearly. We try to be more conscious about our diet, exercising regularly and taking supplements in hopes of fulfilling our vision of better health. We meditate as a way of finding inner peace and new vision. In our own way, we are all trying to improve the quality of our lives by seeing life more clearly. Yet very few of us have considered the role of vision training in expanding our ability to see. That’s what my interest is, and I’ve developed a technology that I feel can really support people in that process.

ATHM: Where can readers go to learn more about resources in this area?

Dr Liberman: There is a lot of information available through the Optometric Extension Program Foundation, OEP.org, and the College of Optometrists in Vision Development, COVD.org. OEP is the organization that started the science of behavioral optometry and vision training in 1928. This is a science that’s been incorporated into the optometric profession for more than 80 years. COVD is the certifying body for doctors of optometry who specialize in the art and science of vision training.

ATHM: Can you tell us more about the device you created and how it works?

Dr Liberman: The device is called the EYEPORT Vision Training System, and people can find out about it at our website, www.exerciseyoureyes.com. The EYEPORT has been cleared by the FDA and is the first clinically proven device available to the public that improves overall visual performance.

The EYEPORT has a series of alternating red and blue LEDs that the user tracks horizontally, vertically, diagonally, and from far to near and back. Our patent deals with a very specific effect that occurs when the eye looks at red vs when it looks at blue. These colors have opposing effects on the autonomic nervous system as well as the aiming and focusing mechanism of the eyes. Red causes the eyes to reflexively over-focus, while blue causes them to reflexively under-focus.

When you alternately look at red and blue lights, you create rocking action—a rhythmic expansion and contraction, simulating the body’s natural state of flow. There’s a reason we rock babies. It puts them into a state of ease. If you close your eyes and tune into your body, you will notice that the most fundamental rhythm is that the body continually expands and contracts—the breathing cycle.

If you go a little deeper into the body, you will notice that same continual expansion and contraction in the heart. That rhythm is then transmitted to the vascular system, the organs, the glands, and the cells. The whole body is continually expanding and contracting. We say the only constant is change—that’s called flow. When that’s going on, the body is in a state of physiological coherence.

Every time we think, try hard, or put effort into something, the breath is momentarily held and restricted. When that occurs, the muscles get tight, mind-body integration is broken, and one’s visual field begins to collapse. We see less, experience less, and become less efficient because the flow is gone. What is the flow? The flow is what’s described and defined by the statement, “The only constant is change.” It’s the homeodynamic heartbeat of the human energy system.

By viewing the alternating red and blue lights on the EYEPORT, you create an involuntary expansion and contraction within the eye and the nervous system, reminding the body of its most primal rhythm and natural state of flow.

And while the system is expanding and contracting, the eyes are simultaneously aiming, focusing, tracking, and teaming, which means these skills are being trained and reinforced without effort. It’s occurring within a state of flow. When this occurs for an athlete, they’re “in the zone.” And when they’re in the zone, something special happens.

The most important aspect of our technology is that it encourages and allows the mind-body system to re-experience its natural state of flow, while visual function is enhanced. This is extremely important because when the mind-body is in a state of flow, it’s at its maximum potential and re-experiences its ability to function and perform without effort.

ATHM: How successful has the system been?

Dr Liberman: So far, we have 3 published studies in peer-reviewed journals, all of which demonstrate that using the device for less than 10 minutes a day—five 90-second exercises—significantly improves visual attention; reading efficiency and comprehension; aiming, focusing, tracking, and teaming of the eyes; speed and span of perception; dynamic depth perception; marks-manship; and sports performance.

That’s what the studies have demonstrated, whether the subjects are medical school students, Little League baseball players, or police recruits. We’ve also completed a pilot study at a university dealing with using the EYEPORT on kids who have
been diagnosed with ADHD. Even though it was only a pilot study, we found statistically significant improvement in visual attention and focusing ability after using the device less than 10 minutes a day over 3 weeks—which means that these children used the EYEPORT for less than 3 hours total. The other thing that's really interesting is that most of the change remains even after you stop using the device. If you go to the gym and exercise your muscles, if you don't continue to exercise them, they become flaccid after awhile. In vision training, it is important to recognize that the eyes are direct frontal extensions of the brain. When you train the eyes, you're directly training the central nervous system. So you don't have to do this for the rest of your life. That's extremely important to me because if you have to do something for the rest of your life, there's a good chance you won't do it. You see, if it takes effort to create change, it will take effort to maintain it. And if it takes effort to maintain it, you can pretty much be assured it will not be maintained because the body, just like the universe, functions by the law of parsimony—it uses the least amount of energy to get the job done.

When the subjects who took part in our studies were reevaluated 3 weeks afterwards, the level of performance was frequently just as high as and, in some cases, higher than it had been immediately after the study. In other words, if the treatment is really working, one's vision and performance should continue to improve, not decline again. I don't want people to have to do something for the rest of their lives to get the benefit. I haven't done vision training in 31 years. I did it in 1976 and something changed about the way my vision worked and the way my brain was responding, and it has continued to improve. I do not see my vision getting worse; I actually see it getting better. That's interesting at 60. You don't expect that.

ATHM: How do you explain that?

Dr Liberman: When you create greater balance between the eyes, you create greater balance in the brain and in the person's ability to find balance in his or her life. Because you're training the brain, you're basically creating new, neuronal connections within the brain, and once people start using these skills the mere act of looking, reading, paying attention as they're driving, sitting in the classroom, or playing golf—whatever they're doing—continually reinforces the skills that they have learned.

The device comes with a 3-month protocol that gives you the exact exercises to do every day. However, all of our studies were based on using the product less than 10 minutes a day, 6 days a week for 3 weeks. Recently, we started a large-scale study with the Washington State Criminal Justice Training Commission where we are incorporating the EYEPORT into police recruit training because we find that the recruits respond much faster, much more accurately, and much more appropriately. We're talking about enhancing performance in everyday life, but when someone is in a stressful situation, like police officers are, they can't afford to respond inappropriately. It could mean their lives or the life of someone else.

Eventually, we want to introduce this into the armed forces, so that people who are under high levels of stress can rely on their vision to respond quickly, accurately, and effortlessly, allowing them to respond more appropriately regardless of the situation they're in. We're trying to introduce not only this device but the concept of spending a couple minutes each day optimizing visual function so that your eyes can guide you in the best possible way. So much of our success in the world is related to how we see and respond to life. When we optimize vision, we optimize our ability to perform. And when we optimize our ability to perform with minimal effort, we experience greater self-respect.

This is especially true with children. One of our published studies was with a group of 12-year-old boys on a Little League team that was in the lowest division in their group of baseball teams. These kids used the device exactly as I mentioned, less than 10 minutes a day for 3 weeks. They didn't practice individually, or as a group, and they had no games over this 3-week period.

At the end of the study, the average player had a 90% improvement in batting performance. Not only that, but the team went from the lowest division to winning the championship. Several of these children started doing better in school as well. Some people think, "A kid can hit the ball better. How big a deal could that be?" But when you don't experience success early in your life, as I didn't in my schoolwork, it can really damage your sense of self. In my personal experience, it wasn’t until sometime in my 40s that I began to recognize that I was actually gifted in certain areas. I no longer have the reading problem that I had as a child, but at the time it really affected me.

Over the past 35 years of doing this work, I have had the pleasure of working with thousands of people. Many of them
notice a change after a single session. They can literally feel their eyes working in a different way. One of the greatest values of vision training is that it allows you to discover that eyesight is only a small aspect of how we see. It also allows you to see that you’re not always looking where you think you’re looking.

For instance, let’s say that you’re playing golf, and you want to putt the ball into the hole. Most people assume that they’re looking at the spot on the ball that they want to hit. However, most of the time, that’s not the case.

I started doing research on this in 1976 and discovered that about 70% of the population is not looking where they think they’re looking. Most people are actually looking a little closer to or further away from where the ball really is. And that’s why most people don’t sink the putt or hit the home run more often. The unfortunate thing is that none of us can see how we’re seeing, so we have no idea why our performance is less than expected.

Another example of this same phenomenon is a group of people at an archery range. They all want to hit the bull’s eye. They’re sure that they are looking at the bull’s eye, and they try hard to aim for its center. Yet very few of them actually hit the bull’s eye. Isn’t this the experience many of us have? We not only miss the bull’s eye on the archery range, but often also in our lives.

One of the beauties of vision training is that it creates a high level of congruity and alignment, so that your physical eye and your mind’s eye are both focusing at the same point at the same time. When this occurs you experience a greater sense of timing and accuracy in everything you do. You start hitting the ball on the sweet spot more consistently and experience greater success at whatever you’re doing because there’s greater focus and clarity in your life.

ATHM: You’ve elevated the whole conversation of vision from a visual organ system to a psycho-emotional experience and even to a spiritual organ.

Dr Liberman: There is no question about that. When we talk about enhanced awareness or expanding consciousness, what are we talking about? We’re talking about seeing things more clearly. Now, for some reason or other, we do not recognize that that level of seeing is inseparably connected with the seeing we’re doing every day. But they are connected. They are absolutely connected because the thing that is seeing is not the eye; it’s something much deeper. The eye is just one part of the process.

Vision and seeing are right at the heart of every spiritual tradition. Meditation is all about focusing on something. People do not connect that practice with the eyes, but whether the eyes are open or the eyes are closed, when you focus on something, your eyes also focus on the same thing. There’s no way to separate these functions.

We must begin to look at vision in a broader way because our eyes guide every move we make. The way we see, where we perceive things to be, how accurately we judge distance and the speed at which things are moving—all of those factors are reflected in our moment-by-moment response to life. Real vision is the ability to respond automatically, without thought or effort.

When that happens, our potential is expanded in ways that I cannot even describe. Improving visual performance directly affects performance on every level, but if you can significantly improve attention, reading, learning, and comfort of everyday use of the eyes, all of that together has a far greater effect on how we feel about ourselves in the world. We can trust our vision to allow us to see situations in life more clearly. And when we see more clearly, we respond more accurately. We begin to trust our vision and ourselves, and that makes huge changes in our lives. If we begin training our vision as children, the effects stay with us through adulthood and permeate our lives.

By doing a few simple vision exercises, you can begin to experience your potential in a whole new way. I know this not only from my own experience but because I’ve had the pleasure of working with thousands of adults and children over the past 35 years. And I’m not the only one. There are probably 6 thousand to 8 thousand behavioral optometrists around the country who also specialize in this work and have similar experiences.

We are beginning to recognize the importance of this work because there’s such an epidemic of vision deterioration. Additionally, children are experiencing more visual problems in the classroom in terms of reading and learning, and almost 90% of
computer users complain about their eyes. It’s time to redefine what it means to see and to incorporate techniques into our everyday life that can preserve our vision and also expand its potential.

ATHM: You’ve taken us into a visionary journey that’s both extremely practical and, I believe, powerfully sacred. Do you have other recommendations you would like to share?

Dr Liberman: It’s very important, for instance, for children to have comprehensive vision examinations. I recommend they see a behavioral optometrist because a behavioral optometrist specializes in preventive vision care and looks at vision not in terms of eyesight but in terms of performance. It’s also important to check the health of the eyes, and optometrists are licensed to do that. But pathology is not very common in children. What is important to a child’s vision is that it’s working properly, that it’s developing properly, and that the child is able to use it effectively. It is imperative that we think preventatively because hardly anyone escapes this epidemic. In Asia approximately 87% of kids aged 16 years and older are near-sighted. That’s huge. There isn’t a disease process in the world that effects so many people.

Vision training and the preventive use of stress-reducing lenses must be used with all children, starting at an early age. It isn’t a question anymore of, “If my child needs glasses, there’s something wrong with his eyes.” No. Children need special kinds of glasses because we don’t want anything to go wrong with their eyes. We recommend nutritional supplements and good eating habits in order to prevent disease, not just remediate it once you have it. Vision training is used in the same way. However, since you are working with the body’s navigational system, the effects can be profound.

ATHM: It sounds like there is a spiritual tie-in to all of this. Do you feel that is the case?

Dr Liberman: Yes. The thought that keeps coming through is that in our own way we are all trying to “see through the eyes of God.” Whether we are religious or think of ourselves as spiritual seekers, we are trying to see things more clearly and be more in alignment with the source—whatever the source is for each of us.

ATHM: It seems as though you’re pointing to the next paradigm of how we view the body. For a while we saw the body exclusively as a biologic machine. More recently, we’ve been looking through the mind-body lens. Now you’re pointing to seeing the body as part of the sacred domain.

Dr Liberman: For many years scientists and clinicians working in the field of mind-body medicine have spoken about the effect of the mind on the body. It’s the foundation of the field of psychoneuroimmunology. I can understand how the mind can effect the body if you identify yourself as the thinker of the thoughts you are experiencing. However, what happens if you do not identify yourself as the thinker but merely the observer of those thoughts as they enter your field of awareness? From my experience, the only reason we are aware that thinking is occurring is because we are observing that process. We are not the thinker; we are that which is aware of the thinking. The significance of this is the realization that our essence is a field of awareness. We are the seeing mechanism I have been discussing. When we discover this, we truly discover what it means to see.

Marc David is an associate editor of Alternative Therapies in Health and Medicine. Suzanne Snyder is managing editor of ATHM.
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