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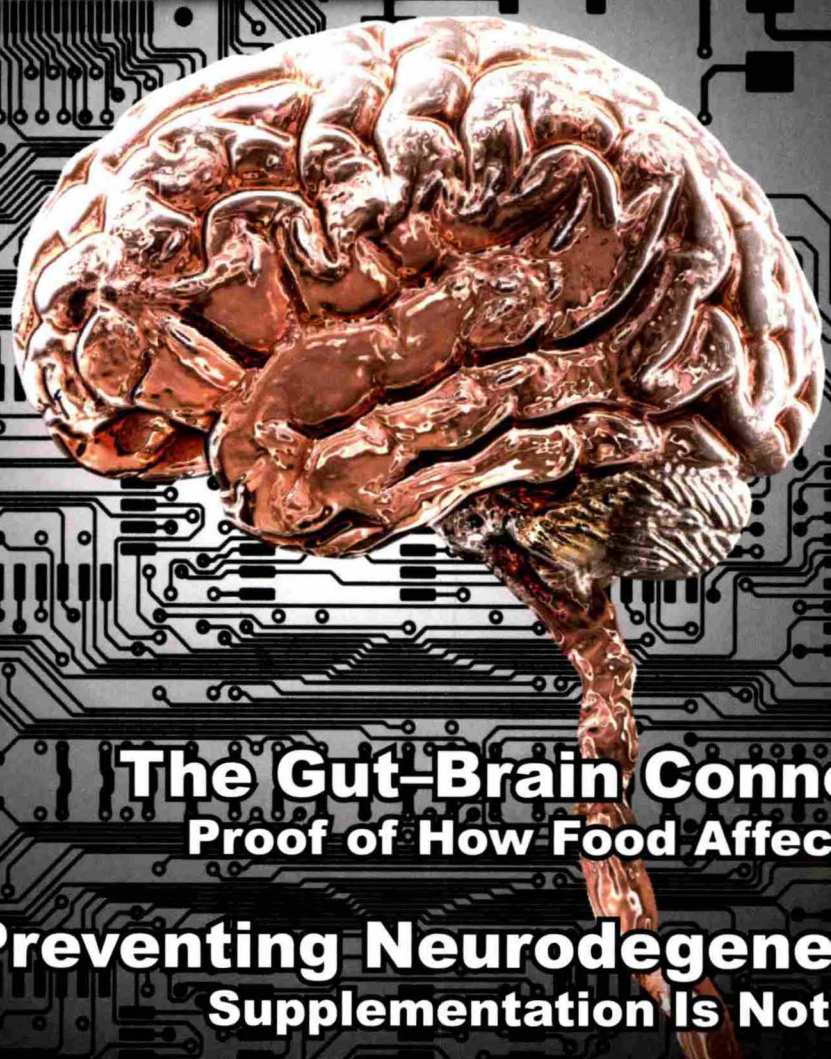
New Look at an Old Treatment

Managing Sepsis
Hospital Administration of IV Vitamin C



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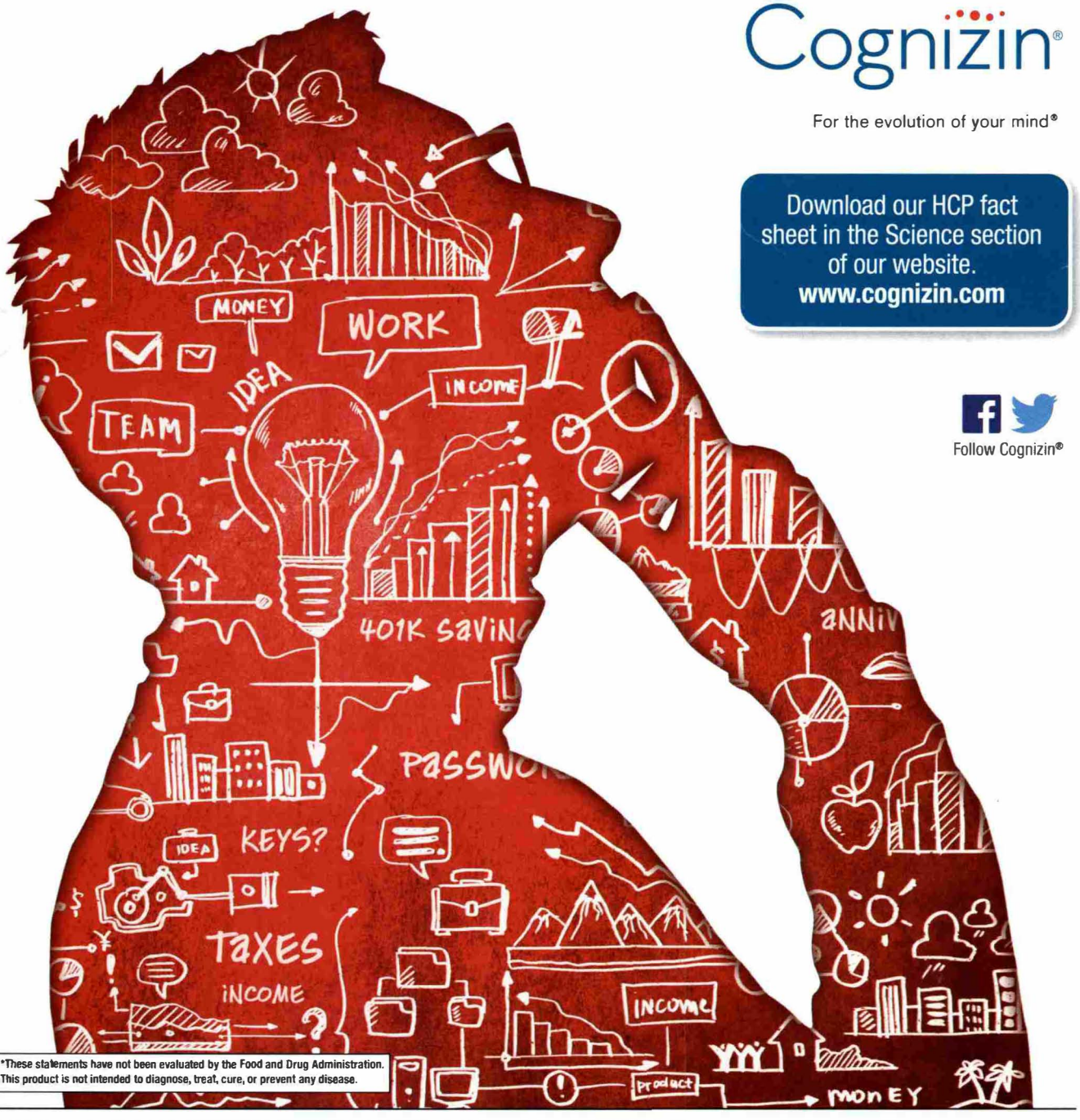

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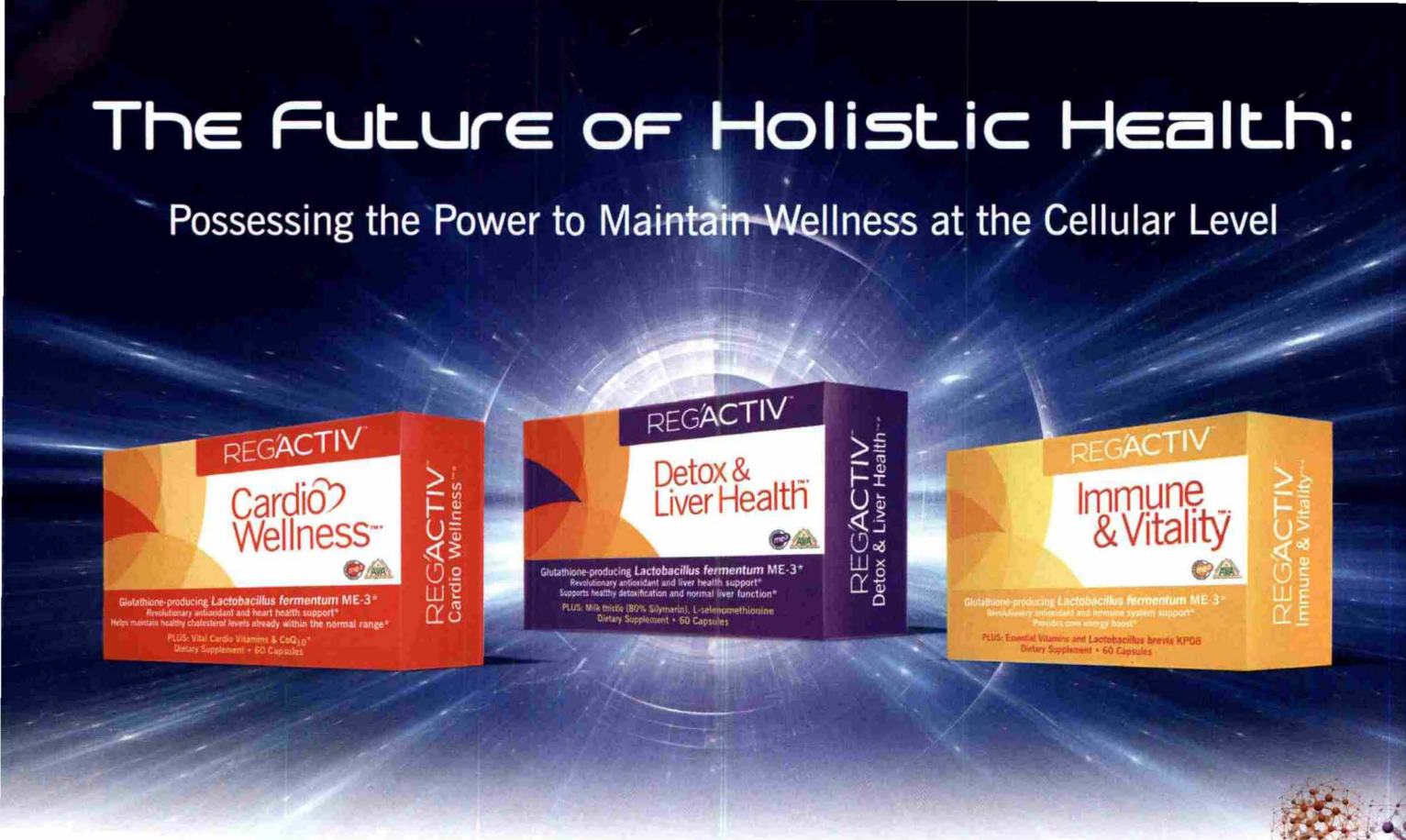

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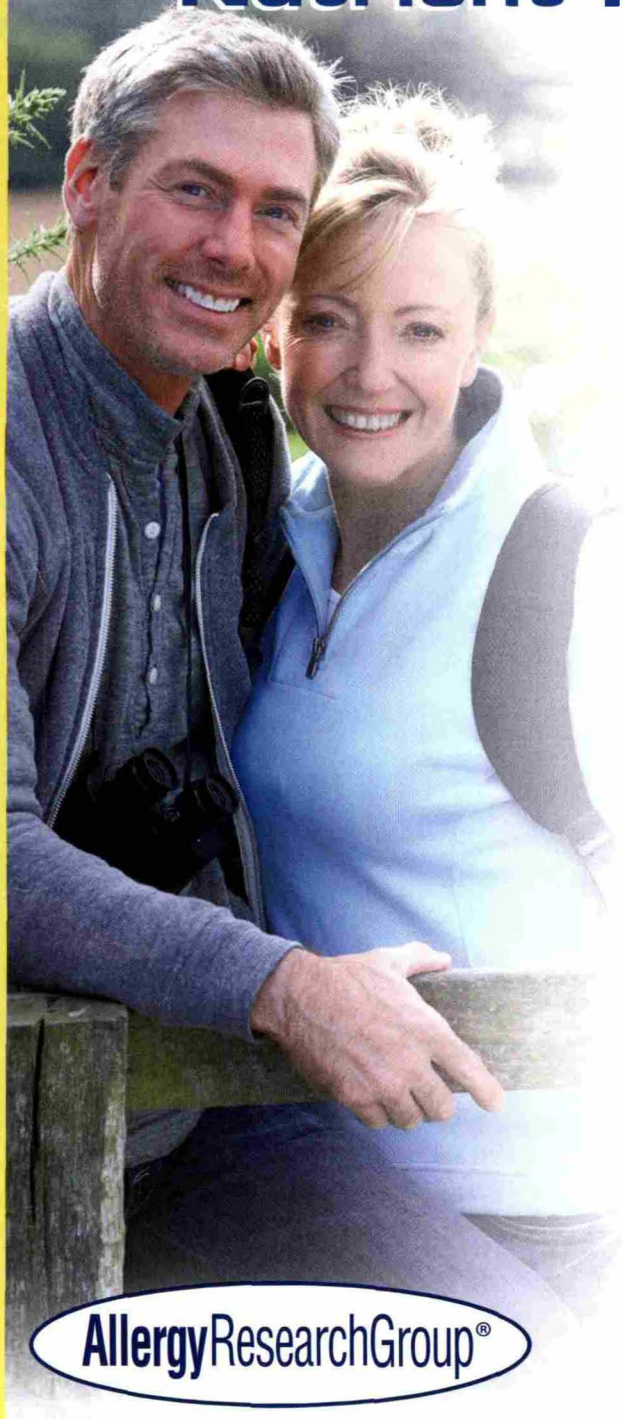

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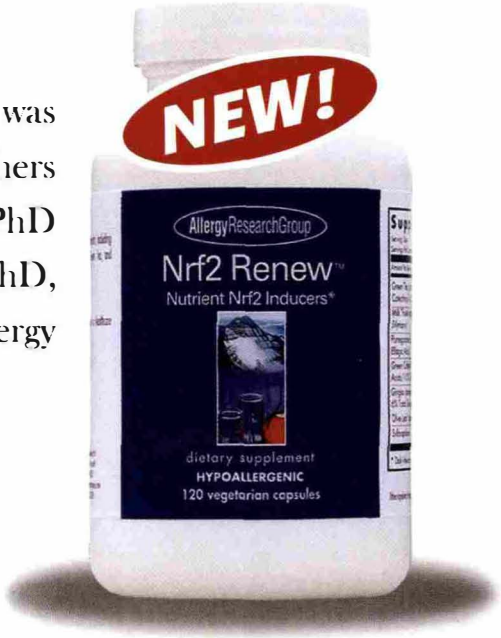

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From the Publisher

Nicholas Gonzales, MD, Passes

Dr. Nicholas Gonzales, a leading alternative cancer physician in New York City, died from an apparent cardiac arrest on July 21. His death was unexpected, given that he was in good health and not being treated for a heart condition. Gonzales's patients will continue to receive his specialized treatment protocols under the care of his partner, Dr. Linda Isaacs. Gonzales was a proponent of the cancer treatment theory of dentist William Donald Kelley. Kelley, who claimed to have cured himself of pancreatic cancer by using a specialized diet, pancreatic glandular supplements, and enzymes, developed a unique system of nutritional metabolic cancer treatment. Gonzales, trained in immunology at Cornell and Sloan Kettering, studied Kelley's theory, protocols, and cancer cases, and treated patients employing Kelley's protocols. He observed early in the 1980s that many different cancers were responsive to the specialized diet and intensive pancreatic supplementation. Gonzales's work was so well thought of that it was considered an important treatment to review by the US Congressional Office of Technology Assessment. Its study of unconventional cancer treatments was published in 1989.

Gonzales submitted more than 100 of his pancreatic cancer case histories to the NIH Cancer Division for review. His treatment success for pancreatic cancer was better compared with patients who received only conventional care. Gonzales and Isaacs refined and modified the Kelley protocols, developing improved regimens that had demonstrable results in a wide range of malignancies.

The cancer establishment, as expected, criticized his work, and Gonzales was frequently investigated. He persevered and his center treated thousands of patients. In the past few years, *60 Minutes* interviewed him; Diane Sawyer attempted to belittle his work, but Gonzales held his own. He was frustrated by a negative review of his

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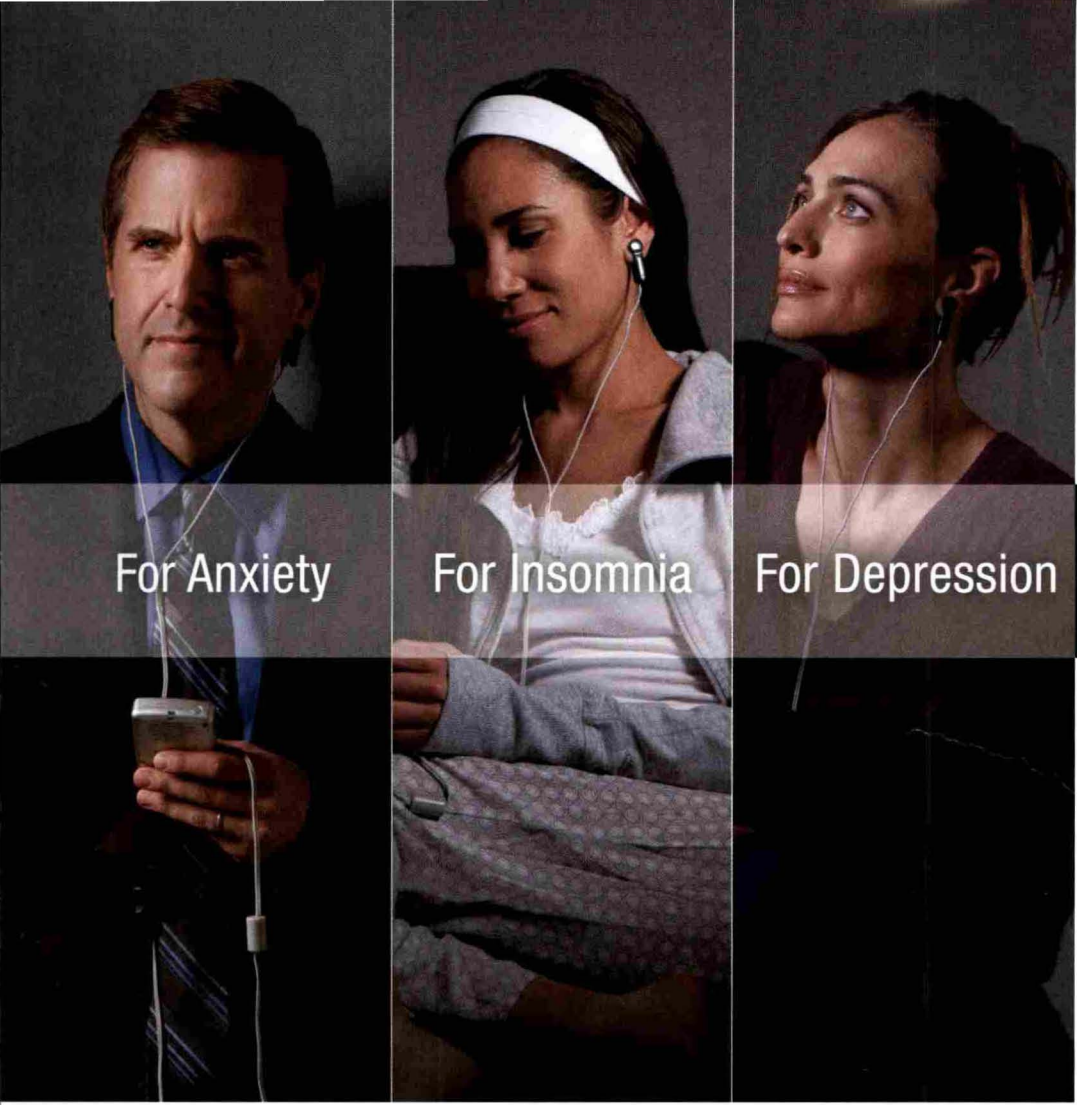

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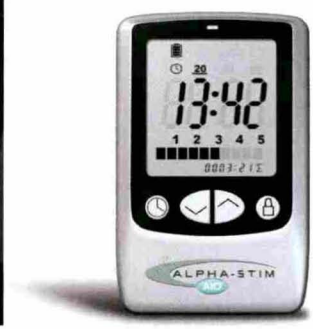

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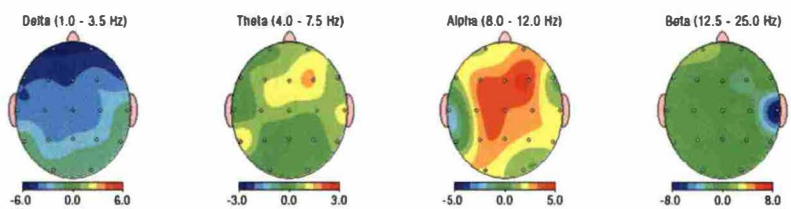

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*Kennerly R. Changes in quantitative EEG and low resolution tomography following cranial electrotherapy stimulation. PhD Dissertation. the University of North Texas. 2006;529 pp., 81 tables, 233 figures, 171 references.

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Letter from the Publisher

➤ continued from page 6

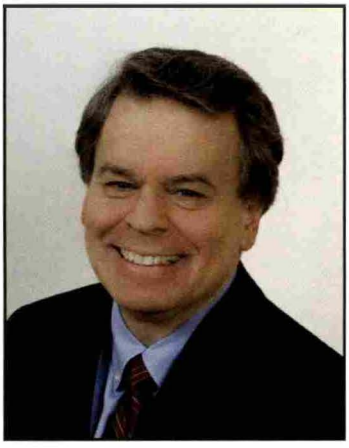
work conducted by a urologist at Columbia University and unsuccessfully attempted to coerce a retraction.

Gonzales was personable and very highly respected; he will be deeply missed by his patients, friends, family, and colleagues.

Recent Deaths of Alternative Medical Practitioners

Beside Gonzales, in mid-June another MD, Dr. Jeff Bradstreet, died – but not of natural causes. Bradstreet was found dead in a North Carolina river by a supposedly self-inflicted chest gunshot wound. Bradstreet practiced medicine in Georgia and Florida; it is unclear why he was in North Carolina. The family disputes the claim that this was a suicide; however, police have not deemed it a homicide. The authorities, weeks before his death, apparently raided Bradstreet's medical practice; details of why he was being investigated have not been made public.

Bradstreet was well known for his anti-vaccination stance. According to Natural News, he was particularly critical of the MMR vaccine, linking it to the increasing epidemic of autism.[1] Bradstreet has children with autism; he devoted much of his practice to studying autism and its causes. He testified at the US House of Representatives about the vaccine–autism connection. Furthermore, according to Natural News, Bradstreet had been working with an unapproved treatment for cancer known as GcMAF (globulin component macrophage activating factor).[2] GcMAF has been touted as a nontoxic immune-system booster effective in the treatment of cancer, AIDS, and other conditions. However, the "miracle" nature of GcMAF has set off alarm bells for the medical authorities; importation of GcMAF has been banned. Natural News as well as other alternative medicine reports have charged that not only was Bradstreet murdered, but his murder was instigated by his unconventional medical work.



Dr. Nicholas Gonzales

Bradstreet's death, however, is not the only mysterious death of an alternative practitioner this summer. Teresa Sievers, another doctor practicing holistic medicine in Florida, was attacked and killed in an expensive neighborhood near where she lived, according to The

continued on page 10 ➤

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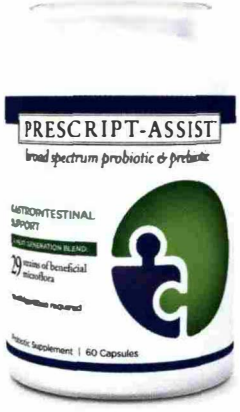

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[1] Pennisi, E. (2011). Body's Hardworking Microbes Get Some Overdue Respect. *Science, 330* (December 2010), 1619.

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Letter from the Publisher

➤ continued from page 8

Free Thought Project.com.[3] Further details of Sievers's murder are that she had been murdered by head trauma with a hammer, but the police have no suspects, according to Natural News. Sievers was the parent of two young daughters; local authorities are puzzled about why she had been so brutally slain. Bruce Hedendal, DC, PhD, of Miami Beach, was also found dead, of unknown causes, in his automobile on June 21. Hedendal strongly advocated and used alternative therapies with his patients and was known for his anti-vaccination stance. Two other physicians practicing integrative medicine in separate areas of Florida, Dr. Barron Holt and Dr. Lisa Riley, also died in the same time period.

Natural News and other e-reports have suggested that there is a conspiracy to kill these alternative medical practitioners. However, the only active homicide case is Sievers. She may have been the victim of domestic violence. Bradstreet does appear to be the victim of foul play, but the authorities have not deemed his case murder. As for the other doctors, might there just be a coincidence that a number of practitioners just died of natural causes in the same time period? Alternative doctors frequently face persecution by medical boards and insurance companies, but it is not reasonable to think that these practitioners were all targeted.

Sepsis in the Hospital and Intravenous Vitamin C

One of the earliest "unproven" treatments that I used in my medical practice was the administration of intravenous ascorbic acid. IV vitamin C was a major component of the "Myers cocktail," an IV push of vitamin C, calcium, magnesium, and B vitamins, used to treat adrenal gland fatigue. Vitamin C, additionally, was administered in high doses in an IV drip over 1 to 2 hours for acute and chronic infection, inflammation, chronic fatigue, and cancer. Frederick Klenner, MD's articles in the 1950s on the management and treatment of polio using intravenous ascorbic acid pioneered its use. Similar papers reporting effectiveness of IV ascorbic acid appeared in the ensuing decades by practitioners in the US and abroad. Ascorbic acid was a remarkably safe treatment and could be administered in very high doses intravenously compared with when it was used orally. However, Robert Cathcart, MD, treated patients with high doses of vitamin C both intravenously and orally; he advised the use of oral vitamin C to "bowel tolerance," enabling round-the-clock vitamin C treatment. The 1979 study by Ewan Cameron, MD, and Linus Pauling, PhD, reported that intravenous vitamin C improved survival of cancer patients. While Charles Moertel at the Mayo Clinic attempted to disprove Cameron and Pauling's work with placebo-controlled studies in the 1980s, Pauling's review of Moertel's data revealed that the

continued on page 15 ➤

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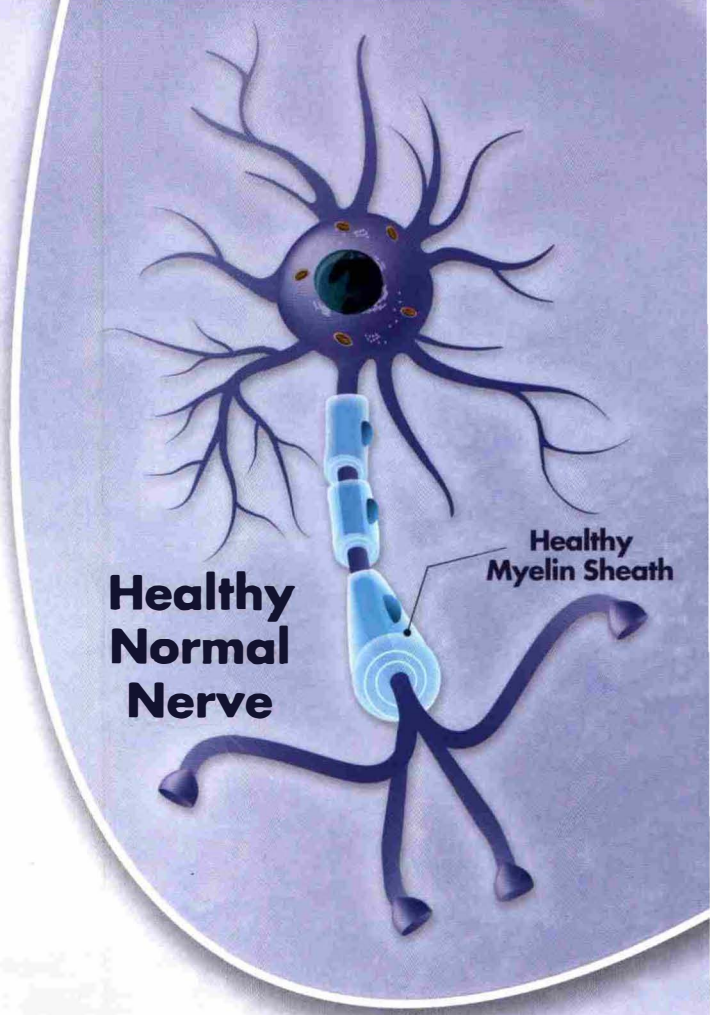

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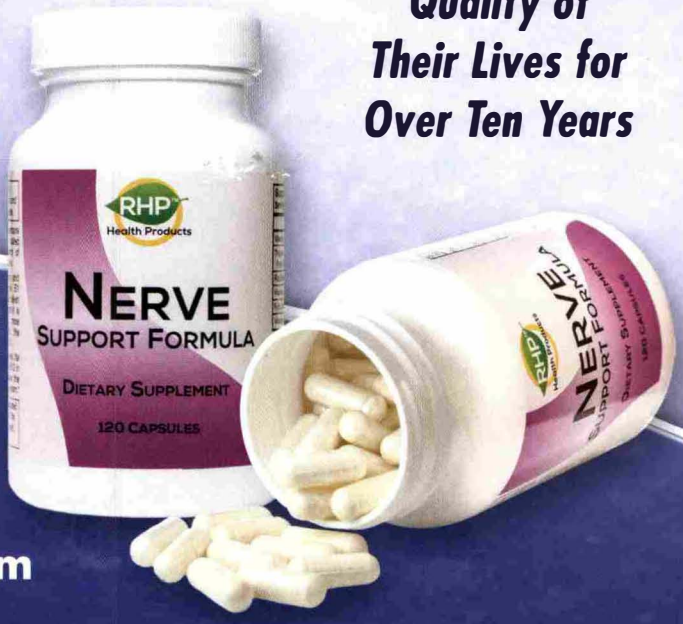

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Disclosure: The *Townsend Letter for Doctors & Patients* publishes information about alternative medicine written by researchers, health practitioners, and patients. As a forum for the entire alternative medicine community, we present information discussing a wide variety of alternative and integrative medicine practices. In addition to publishing original research and literature abstracts and reviews, we encourage case studies and anecdotal reports. Detailed anecdotal reports are not viewed as proof but as possibilities that need further investigation. All authors are required to submit their reports to other professionals for review and include proof of peer-review with article submission.

The editors of the *Townsend Letter* recommend that all patients (and physicians) review further reports provided in the article's references and investigate the practitioner's techniques before undertaking an alternative diagnosis, examination, or treatment. Please discuss such treatments and examinations with a reputable health practitioner in your community. If you do use an alternative treatment discussed in the *Townsend Letter*, we would appreciate your report of the outcome, any side effects, and costs.

majority of patients treated with ascorbic acid did indeed have improved morbidity and greater survival.

Although the biochemistry, mechanism of action, and physiologic activity of ascorbic acid have been extensively reported in the literature, as detailed in book compilations by Thomas Levy, MD, the medical profession has largely ignored ascorbic acid's role in the treatment of patients experiencing severe infection and sepsis in the hospital setting. The *Townsend Letter* is pleased to publish an interview by Kirk Hamilton, author of *Expert Interviews* and the *Clinical Pearls Database,* of Alpha Fowler, MD, professor of medicine at the Virginia Commonwealth University School of Medicine, on the use of high-dose intravenous ascorbic acid in sepsis. Fowler and his colleagues have been studying the use of parenteral ascorbic acid in experimental animals with sepsis. Their studies published during the past 5 years have shown that animals treated with vitamin C had greater survival, reduction in inflammation markers, and less organ failure.

In 2014 Fowler and his colleagues published a phase I safety trial of IV ascorbic acid in humans with sepsis.[4] The vitamin C was administered in relatively low doses compared with what most physicians use in their integrative practices. The study was placebo controlled, with treatment arms of approximately 1000 mg and 3500 mg administered in D5W every 6 hours. Compared with the placebo, dextrose in water, septic patients in both treatment cohorts had greater survival and reduction in inflammation. Additionally, the patients who were treated with the higher dose of IV ascorbic acid had the best outcomes.

Fowler's work, published in the *Journal of Translational Medicine*, is transformational – an "unproven" treatment becomes nearly "proven." He intends to organize a multi-institution, placebo-controlled, phase II study of IV ascorbic acid in sepsis. His paper should be shared with physicians and nurses in the ICU and the pediatric ICU at every hospital.

Lithium's Role in Brain Health

In the late 1800s, medicine came to appreciate the stimulating pharmacologic effect of cocaine; it eventually was manufactured as a drug to be used in a variety of procedures. Around the same period, a soft drink manufacturer created a cola drink – popularized, undoubtedly, by the inclusion of cocaine. Only in the 1950s did Coca-Cola remove cocaine from its proprietary recipe ingredients. Early in the 20th century, another manufacturer created a lemon-lime soda that was also highly acclaimed by the public. 7 Up was a tasty option for individuals wanting a non-cola pop; however, some of 7 Up's acclaim may have been due to the inclusion of the mineral lithium. Like Coke, 7 Up removed lithium from its recipe in 1950. Cocaine's effect on mood was widely appreciated; lithium's, not so much. However, before lithium came to be known as a psychiatric drug, it had a widely touted reputation of ameliorating gout, long before the drug allopurinol was patented. However, in the 1940s, when the medical profession began to counsel reducing sodium intake, the substitution of lithium salts was advised instead. Unfortunately, some individuals overdosed on lithium salts, poisoning themselves. In 1949 an Australian physician observed that lithium could be a potential treatment for a severe psychiatric disorder, manic depression. It would be another 20 years before the FDA approved high-dose lithium for psychiatric treatment in the US.

While high-dose lithium has remained a mainstay drug for manic depression, it has been fraught with treatment failure as well as potential adverse effects, not the least of which is kidney toxicity. In this issue of the *Townsend Letter*, James Greenblatt, MD, reports on the medical use of "low-dose" lithium. Greenblatt is an assistant professor of psychiatry at Tufts University School of Medicine and chief medical officer at Walden Behavioral Care in Waltham, Massachusetts. Greenblatt's use of low-dose lithium has had remarkable success in treating many psychiatric conditions in adults and children, with minimal adverse effects. Greenblatt also reports on lithium's use in the preservation of memory and its role in the treatment of dementia.

***

Also be sure to read the brilliant article by Nicola Ducharme, ND, "'Lyme Brain': Causes and Solutions." She theorizes that cognitive dysfunctioning follows from the brain's exposure to the pathogen, demyelination, inflammation, and neurotoxin exposure. Ducharme suggests that a variety of non-drug agents that will calm and rebuild the "Lyme brain."

Jonathan Collin, MD

Notes

1. Wilson J. Ex-Merck employee turned anti-vaccine activist now terrorized by Big Pharma Black Ops branch [online article]. NaturalNews.com. Aug. 10, 2015. http://www.naturalnews.com/050728_Big_Pharma_black_ops_Merck_employee_Brandy_Vaughan.html#ixzz3iSlfE9wn.
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3. Vibes J. 3 alternative health doctors found dead in the last 2 weeks after run-ins with the Feds [online article]. The Free Thought Project. thefreethoughtproject.com. July 2, 2015. http://thefreethoughtproject.com/3-alternative-health-doctors-dead-run-ins-feds.
4. Fowler AA 3rd, Syred AA, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl. Med.* Jan. 31, 2014;12:32.

◆

ILADS Foundation Names MacDonald as Award Recipient

The International Lyme and Associated Diseases Educational Foundation (ILADEF) is delighted to announce Lyme disease research pioneer Alan B. MacDonald, MD, as the 2015 ILADEF Pioneer in Lyme Award Dinner recipient for his groundbreaking studies in Lyme and associated diseases. The board will honor MacDonald at an intimate dinner on Thursday evening October 15, 2015, at the Marriott Harbor Beach Resort, Ft. Lauderdale, Florida.

MacDonald's brilliant career has spanned more than four decades of seminal research. In the late 1970s, he worked diligently to create tests to detect the newly discovered pathogen *Borrelia burgdorferi* (Bb). He was among the first researchers to study Bb in humans and the first to publish evidence of Bb cystic forms, granular forms, and cell wall deficient forms. MacDonald has also done groundbreaking research on the potential connection between Lyme and Alzheimer's diseases. Through his research, and with the help of other leading researchers in the fields of molecular and cellular biology, MacDonald is continuing to pioneer a broader understanding about the behavior of *Borrelia burgdorferi* as an infectious pathogen.

If you would like to attend this prestigious event, please go to www.ilads.org or contact will.stewart@ilads.org to register. Space is limited.

The International Lyme and Associated Diseases Educational Foundation (ILADEF) was founded in 1999 to promote education and research of tick-borne diseases. Donations to this entity, a 501(c)(3) educational foundation, are tax deductible. The premiere program of ILADEF is the physicians training program. Using designated volunteer training physicians from ILADS, this program has trained several hundred clinicians who are in turn treating thousands of Lyme patients. ILADEF's Research Group also promotes relevant tick-borne disease research projects.

Cleveland Clinic Receives $1 Million Gift to Support Center for Functional Medicine

Cleveland Clinic has received a four-year, $1 million gift from Pure Encapsulations that will support its Center for Functional Medicine. The gift will be used for clinical research, education, curriculum development, community programs, and policy change initiatives.

"A growing number of patients, especially those with chronic conditions, are finding relief with functional medicine, which focuses on the underlying causes of disease," said Dr. Mark Hyman, director of Cleveland Clinic's Center for Functional Medicine. "This generous gift provides us with the opportunity to educate health-care providers, as well as consumers, about the benefits of the functional medicine model."

Functional medicine is based on the evidence that lifestyle factors such as nutrition, sleep, exercise, stress levels, relationships, and genetics are major contributors to disease. Pure Encapsulations produces a line of hypoallergenic nutritional supplements, which are an important component of the functional medicine model.

"We realize the transformative power of the Cleveland Clinic Center for Functional Medicine on our modern healthcare system," said Joy Devins, vice president of Pure Encapsulations. "Pure Encapsulations is ecstatic to have been involved with the center since its inception and to support research, education and community programs that will change the way healthcare is delivered across the globe."

Cleveland Clinic functional medicine physicians are working with specialists to set up four clinical trials studying the effect of functional medicine on the treatment of asthma, inflammatory bowel disease, migraines, and type 2 diabetes.

"In the spirit of innovation, the Cleveland Clinic was the first major, academic medical center to embrace functional medicine, and patients are coming from across the country to be treated," said Dr. Patrick Hanaway, medical director of the Center for Functional Medicine. "This gift will help further our research to show the impact functional medicine can have on patients."

Cleveland Clinic's Center for Functional Medicine opened in September 2014, in collaboration with the Institute for Functional Medicine.

About Cleveland Clinic

Cleveland Clinic is a nonprofit multispecialty academic medical center that integrates clinical and hospital care with research and education. Located in Cleveland, Ohio, it was founded in 1921 by four renowned physicians with a vision of providing outstanding patient care based upon the principles of cooperation, compassion and innovation. Cleveland Clinic has pioneered many medical breakthroughs, including coronary artery bypass surgery and the first face transplant in the United States. *US News & World Report* consistently names Cleveland Clinic as one of the nation's best hospitals in its annual "America's Best Hospitals" survey. More than 3000 full-time salaried physicians and researchers and 11,000 nurses represent 120 medical specialties and subspecialties. The Cleveland Clinic health system includes a main campus near downtown Cleveland; 8 community hospitals; more than 75 Northern Ohio outpatient locations, including 16 full-service Family Health Centers; Cleveland Clinic Florida; the Lou Ruvo Center for Brain Health in Las Vegas; Cleveland Clinic Canada; and, scheduled to begin seeing patients in 2015, Cleveland Clinic Abu Dhabi. In 2012, there were 5.1 million outpatient visits throughout the Cleveland Clinic health system and 157,000 hospital admissions. Patients came for treatment from every state and from more than 130 countries. Visit us at www.clevelandclinic.org. Follow us at www.twitter.com/ClevelandClinic.

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NCNM Introduces New Doctoral Program in Chinese Medicine

The National College of Natural Medicine (NCNM) introduces its newest degree program, the Doctor of Science in Oriental Medicine (DSOM). The DSOM is an accredited, four-year professional doctoral program that integrates modern biomedical science into a comprehensive framework of ancient Chinese medical science and philosophy to achieve enhanced clinical outcomes for practitioners and patients. This is the first doctoral-level classical Chinese medicine degree offered by the college and one of the first of its kind in North America.

The classical approach to Chinese medicine honors the thousands of years of clinical knowledge and experience that in modern times has been standardized into a system called "Traditional Chinese Medicine," the version taught by most Chinese medical schools in the US and abroad. With its focus on the ancient roots of Traditional Chinese Medicine, classical Chinese medicine presents a highly complex system of knowledge that brings balance and healing to body, mind, and spirit through a highly individualized approach to the medicine.

NCNM has been expanding its programmatic offerings to add to its flagship programs in naturopathic medicine and classical Chinese medicine in recent years by launching two undergraduate degrees and master's programs in integrative mental health, global health, nutrition, and integrative medicine research – growing its enrollment 33% since 2007. The college's School of Classical Chinese Medicine has offered a Master of Science in Oriental Medicine (MSOM) program since 1995.

Provost and Vice President of Academic Affairs Andrea C. Smith, EdD, observed that NCNM's new program is one of the most comprehensive and remarkable programs of its type in the world. Said Smith: "NCNM's School of Classical Chinese Medicine was founded to cultivate Chinese medicine clinicians and scholars steeped in the deep wisdom and knowledge codified in ancient medical texts of revered physicians, such as Sun Simiao and Huangdi – knowledge that was nearly lost to the practitioners of today. We are deeply indebted to the school's founding professor, Heiner Fruehauf, PhD, and Dean Laurie Regan, PhD, and our renowned faculty, through whose efforts NCNM is fanning the embers of passion once again for the ancient practice of Chinese medicine – to the benefit of patients throughout the US."

The DSOM is designed to provide students a solid foundation in Chinese medicine theory through an appreciation of the original language of the ancient, classical Chinese medical texts. These texts provide the foundation for training within a broad spectrum of Chinese medicine modalities, including acupuncture and herbal medicine. A strong focus of the DSOM program is the integration of CCM with biomedicine, training practitioners to develop the capacity to communicate, educate, and collaborate within the larger system of health care.

Smith noted that the college's classical Chinese medicine students are mentored by some of the world's leading scholars. Smith said, "We encourage a deep and sustained exchange of inquiry in the classroom that assists our students as they learn to bridge and communicate Eastern and Western ways of understanding health and disease. Upon completion of the DSOM program, our students are prepared to more fully communicate and collaborate with their Western medical colleagues and achieve successful clinical outcomes for their patients."

Visit www.ncnm.edu/DSOM to learn more about NCNM's new Doctor of Science in Oriental Medicine program, or watch a short video about its School of Classical Chinese Medicine at https://www.youtube.com/watch?v=aU-xq7T-7ng.

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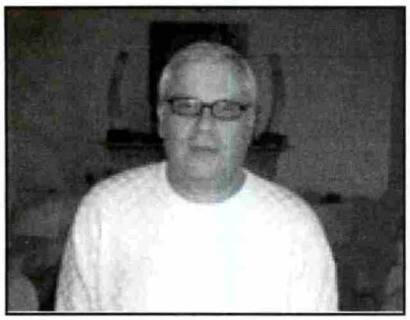

Efrain Olszewer, MD, and Orthomolecular Medicine in South America

by Eleonore Blaurock-Busch, PhD

In Brazil, Efrain Olszewer is synonymous with orthomolecular medicine. In fact, orthomolecular medicine *is* Efrain Olszewer. In São Paulo, a megacity of 11 million people, most doctors are familiar with him. Olszewer brought complementary medicine, chelation therapy, nutrition, and everything connected to orthomolecular and alternative medicine to Brazil and nearly all South American countries.

This energetic man graduated from the University of San Simón in Bolivia, where he also played football, and this love for sport explains his interest in sports medicine. He enrolled in postgraduate courses in internal medicine and cardiology at the Heart Institute, São Paulo University in Brazil. He started his own clinic in 1992, specializing in internal medicine and cardiology. To this day, he has accumulated over 60,000 patient files, remains dynamic and powerful, has in-depth knowledge about most topics in conventional and alternative medicine, can rattle off biochemical information about most subjects, and when he lectures, people hang on his words. He can speak for hours, which he often does, without tiring himself or his audience. He also listens, and when he does, he is attentive, observing, absorbing, and actually quite still.

Olszewer is known in chelation like few others. Most chelationists are familiar with the 28-month retrospective study of 2870 patients, published in 1989 by Carter and himself. This often-cited work (the practical aspects were performed under Olszewer in São Paulo) documented that atherosclerosis and other degenerative and age-associated diseases treated with intravenous disodium EDTA chelation therapy showed great improvement. Using carefully defined criteria, marked improvement occurred in 76.9% and good improvement occurred in 17% of treated patients with ischemic heart disease. Marked improvement was noted in 91% of patients with cerebrovascular and other degenerative cerebral diseases. Of 4 patients with scleroderma, 3 had marked improvement, and 1 had good improvement. Seventy-five percent of all patients had marked improvement in symptoms of vascular origin. Independent of pathology, 89% of all treated patients had marked or good improvement. One can conclude that Carter's and Olszewer's research paved the way for the US TACT (Trial to Assess Chelation Therapy) study.

Olszewer is a workaholic and a family man, not a contradiction at all. According to his wife, he is an avid reader, always seeking knowledge; and when he is not treating patients (and he has one of the busiest chelation practices I have seen), he writes and lectures. He has written 73 books on topics such as orthomolecular medicine, neurotransmitters in obesity, chelation, free radicals, and nutrition in sports medicine, and still accepts phone calls from his patients. "I don't give out my handy number," he says when his phone rings, "but somehow, patients get hold of me at all hours of the day." He sighs, answers patiently.

Patients love him, and so does his staff. No matter how busy he seems, he finds time to pat assistants on the back, asks visitors how they are, in Hebrew-accented Portuguese, Spanish, or English. He is relaxed in a hurried environment, and when his grandchildren come running toward him, he radiates happiness. When he disappears for whatever length of time for another treatment, meeting, or lecture, Melany, his wife, shrugs. "He is the head," she says, "but I am the neck that moves him."

There is more. He is the clinical editor of the *Journal of Orthomolecular Practice*, published every three months since 1993. In 2002, after having taught courses at other schools of higher education, Olszewer founded and still presides over São Paulo's School of Orthomolecular Medicine called FAPES, where thousands of doctors from Brazil and South American countries have enrolled in postgraduate courses in nutrition, chelation, hydrotherapy, sports medicine, you name it. As a result, about 3000 doctors use IV chelation in Brazil, between 500 to 1000 in Latin America. Doctors from Spain, Portugal, and other European countries regularly attend FAPES courses and an estimated 25,000 to 30,000 doctors now use the principles of orthomolecular medicine, and most of this change in medical practice is due to Acting Dean Efrain Olszewer's involvement.

A good number of his postgraduate students attended the 28th Congresso Ortomolecular, held June 19 through 21, 2015; and this event that took place at the Convention Center of São Paulo, reminded me of ACAM conferences in the 1980s. Nearly 1500 doctors from around the world flocked to São Paulo, attentively listening to a long list of international lecturers. El Presidente Efrain Olszewer and his staff made sure that the event ran smoothly. It did.

For more information
about the congress:
congressoortomolecular.com.br.

Eleonore Blaurock-Busch, PhD, is research director at Micro Trace Minerals/Trace Minerals International Laboratories (www.microtrace.eu and www.tracemin.com). She is adviser to the German Medical Association of Clinical Metal Toxicology, and author of many articles and books on diet, nutrition and orthomolecular medicine, and metal toxicology. She has lectured worldwide on these subjects, including at the recent Congresso Ortomolecular in São Paulo. She can be reached at ebb@microtrace.de.

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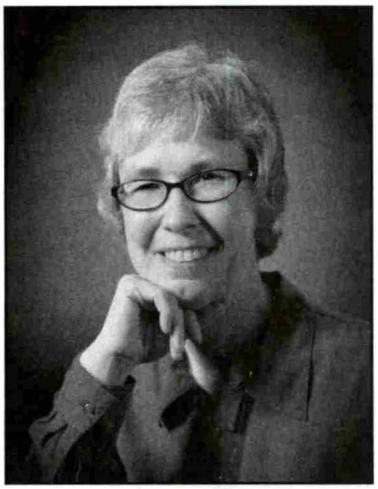
Joel D. Wallach, BS, DVM, ND
Ma Lan, MD, MS, LAc
Gerhard N. Schrauzer, PhD, MS, FACN, CNS

EPIGENETICS

THE DEATH OF THE GENETIC THEORY OF DISEASE TRANSMISSION

Foreword by
Jeffrey S. Bland, PhD



Shorts

briefed by Jule Klotter
jule@townsendletter.com

Cytokines, Inflammation, and Depression

Chronic inflammation and infection can be an underlying cause of depression and anxiety in some people. Cytokines, the chemicals that coordinate immune cells and amplify immune response, also affect the brain and cause behavioral changes. "We know now that several of the behaviors associated with infection, such as increased sleep, decreased appetite, and decreased sexual drive, which are often referred to as 'sickness behavior,' may be at least partly attributed to the specific effects of cytokines," write Ziad Kronfol, MD, and Daniel G. Remick, MD, in their 2000 review article. These behaviors are beneficial when the body is fighting infection or repairing a serious injury. Long term, however, cytokine activity that accompanies inflammation and chronic infection can lead to depression and other psychological illnesses.

In an article for *Scientific American Mind,* German neuropsychology professor Erich Kasten outlines evidence that link depression and other psychiatric conditions with pro-inflammatory cytokines. He points out that pro-inflammatory cytokine drugs used to treat skin cancers and hepatitis C, such as interferon-α, are known to cause depression in patients. Interferon can also produce cognitive impairment, psychosis, and suicidal ideation, according to Kronfol and Remick.

Several studies have found high levels of pro-inflammatory cytokines in psychiatric patients, indicating an underlying infection or injury. A 2010 meta-analysis involving 24 studies found significantly higher blood levels of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in about 400 patients with major depression (Dowlati Y et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. March 1, 2010;67(5):446–457). Both TNF-α and IL-6 are pro-inflammatory. Elevated pro-inflammatory cytokines were also found in 48 patients with panic disorder or posttraumatic stress disorder in a 2009 study led by Elizabeth Hoge. Hoge and colleagues found detectable levels of 6 or more (out of 9) common pro-inflammatory cytokines in 87% of the patients, compared with only 25% of healthy age- and gender-matched controls.

"Chronic inflammation in and of itself almost certainly accounts for only a subset of patients with emotional disorders," says Kasten. "Yet several trials have shown that patients who do not respond to traditional antidepressants frequently begin to improve when they take anti-inflammatory medications, from everyday ibuprofen to cytokine inhibitors, on top of their other prescriptions." Anti-inflammatory nutraceuticals, such as omega-3 fatty acids, may also be helpful.

Kasten E. Can infection give you the blues? *Sci Am Mind*. May/June 2015:46–49.
Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry*. May 2000;157(5):683–694. Available at http://www.fettermanevents.com/files/CytokinesandtheBrain.pdf. Accessed July 18, 2015.

Eye Movement Desensitization and Reprocessing (EMDR) and Trauma

Since its introduction in a 1989 randomized controlled trial, eye movement desensitization and reprocessing (EMDR) has been used for a variety of psychological problems, particularly trauma-induced ones, as well as stress-induced physical disorders, according to Francine Shapiro, PhD. EMDR therapy has standardized protocols and procedures that include history taking, self-care techniques that support emotional stability, and reprocessing with dual attention stimuli. During reprocessing, clients focus on the worst part of a traumatic event, associated negative beliefs, and body responses while performing eye movements, tapping, or toning and then release the memory with a deep exhalation. The thoughts and feelings that arise during a reprocessing session can provide therapists with information for another session, if needed. "Completed processing is posited to involve an alteration of the originally stored memory through a process of integration and reconsolidation," says Shapiro. EMDR produces brain imaging changes, according to a 2005 study involving six police officers with PTSD, as well as significant clinical changes. Most symptoms from a single trauma usually resolve with three to six sessions.

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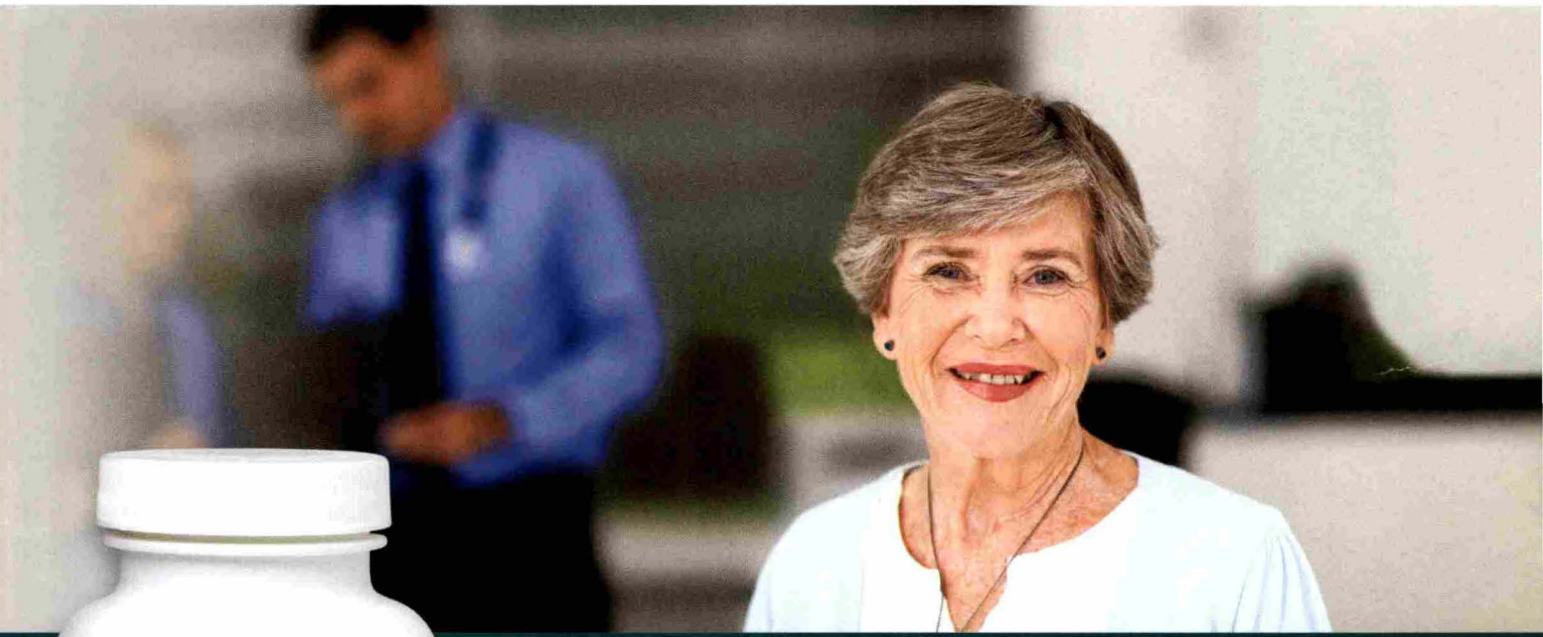

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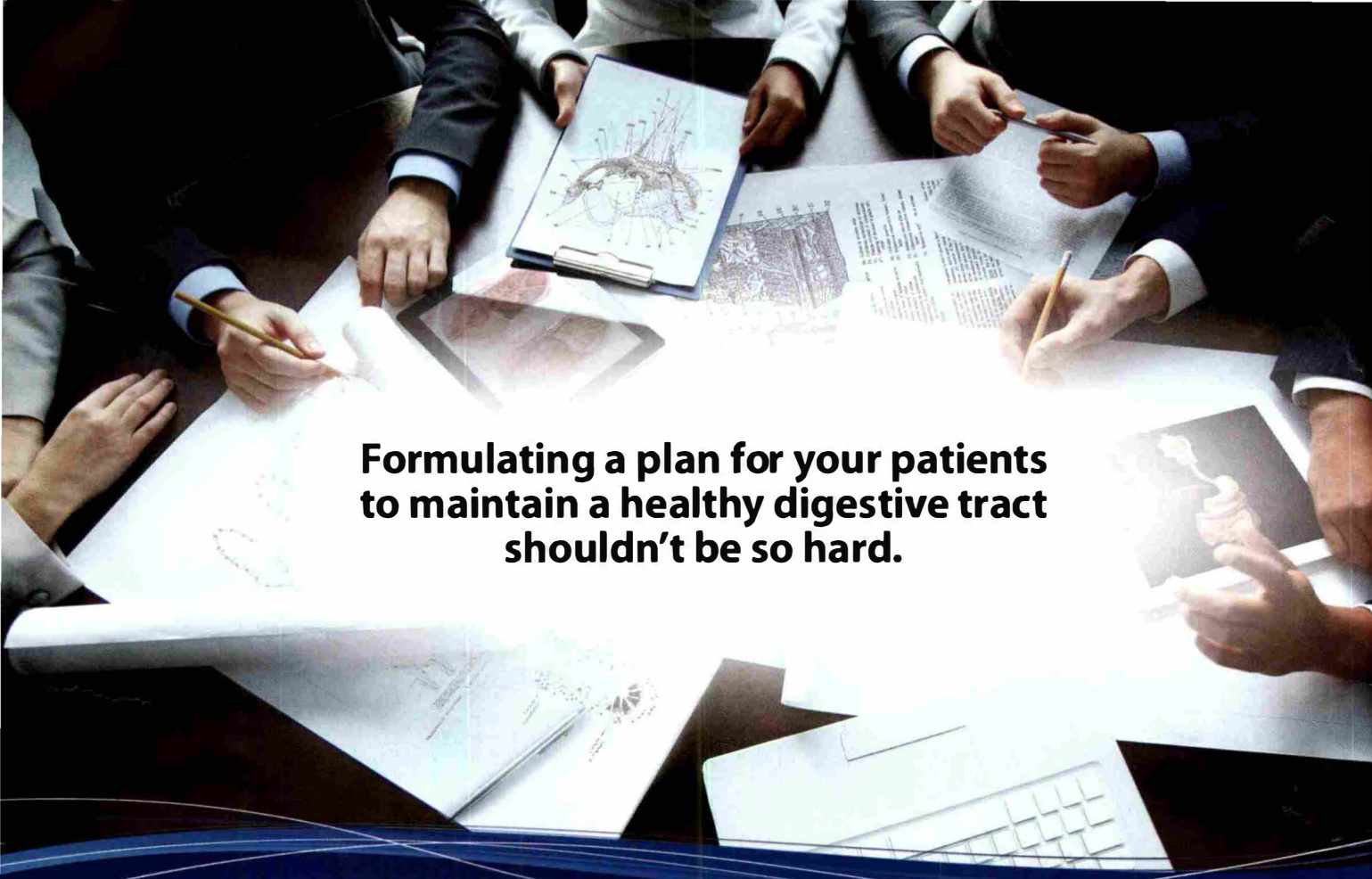

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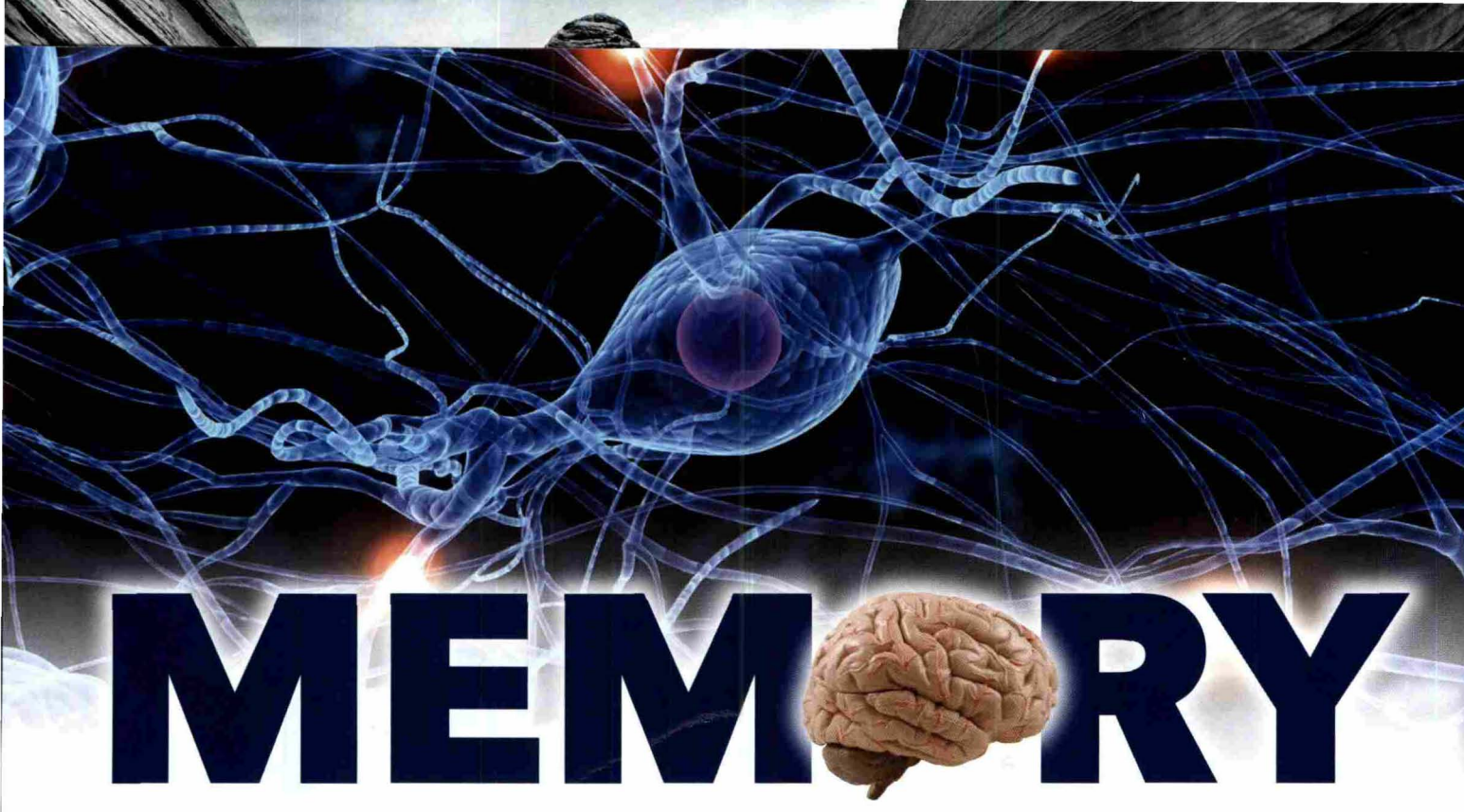

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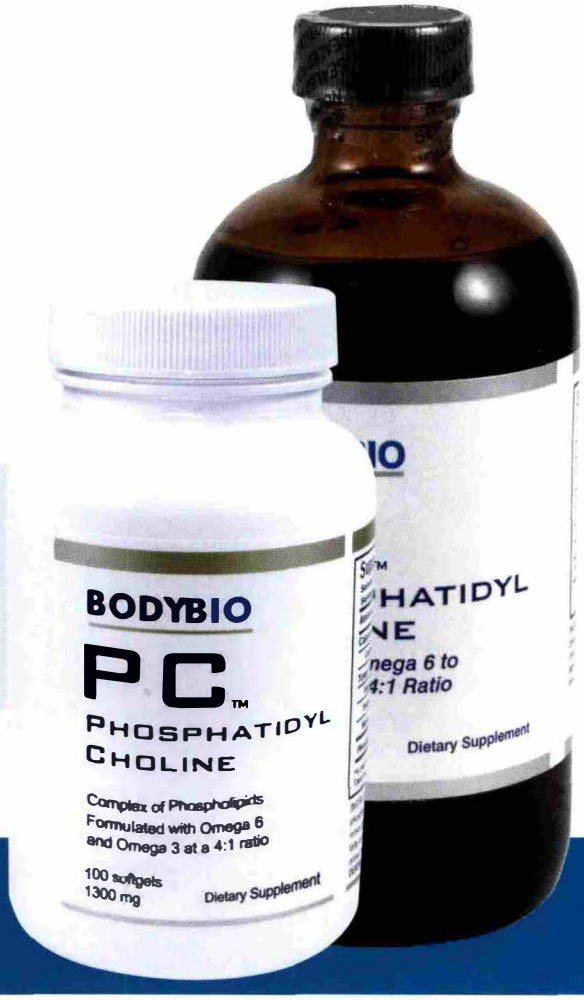

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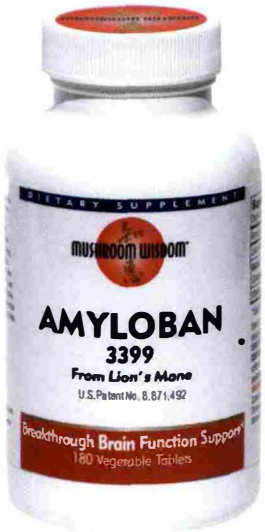

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EMDR's effectiveness for posttraumatic stress disorder (PTSD) has been verified by numerous studies over the years, including a randomized, placebo-controlled clinical trial led by Bessel A. van der Kolk. That 2007 study randomly assigned 88 patients with PTSD to receive 8 weekly, 90-minute EMDR sessions; 8 weeks of fluoxetine (Prozac) treatment; or placebo pill. At 6 months after treatment's end, 75% of adult-onset trauma patients who used EMDR were asymptomatic compared with none in the fluoxetine group. Only 33.3% of child-onset trauma patients who had EMDR therapy were asymptomatic at 6-month follow-up. The authors noted that child-onset trauma usually requires more than 8 sessions. Child-onset trauma patients also had a greater response to fluoxetine at posttreatment assessment than the adult-onset group, but fluoxetine treatment had no effect 6 months after treatment was discontinued.

Although we tend to associate PTSD with life-threatening and violent/abusive events, Shapiro says that posttraumatic stress symptoms can also arise from life experiences such as debilitating illness; the death of a loved one; and problems with relationships, work, or study. She suggests trying EMDR before turning to medication when patients relate their anxiety, depression, hypervigilance, nightmares, insomnia, or anger to a difficult experience. EMDR has also relieved migraine headaches, "phantom" pain, and stress-related skin disorders, such as atopic dermatitis and psoriasis, in clinical studies.

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Shapiro F. The role of eye movement desensitization and reprocessing (EMDR) therapy in medicine: addressing the psychological and physical symptoms stemming from adverse life experiences. *Permanente J.* Winter 2014;18(1):71–77. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3951033. Accessed July 29, 2015.

Van der Kolk, BA, Spinazzola J, Blaustein ME et al. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. *Clin Psychiatry.* January 2007;68(1):37–46. Available at www.researchgate.net. Accessed July 8, 2015.

Lion's Mane and Depression

Lion's mane (*Hericium erinaceum*) is an edible mushroom from East Asia with several medicinal properties including antioxidant, immune-modulating, hypolipidemic, anticancer, and neuroprotective effects. Case reports and small studies from Japan indicate that lion's mane (known as *yamabushitake* in Japan) and extracts from the mushroom might be beneficial for people with depression and psychiatric illnesses. In a 2009 study, dried *yamabushitake* powder (four 250 mg tablets, t.i.d.) significantly improved cognitive function scores in 15 patients with mild cognitive impairment compared with an age- and sex-matched control group. Amyloban 3399, made from amycenone (a standardized lion's mane extract), relieved recurrent depression that had required hospitalization on 5 occasions in an 86-year-old man who could not tolerate the antidepressant mirtazapine. Mirtazapine caused mild cognitive impairment, so his physicians switched him to Amyloban 3399. "After 6 months, the cognitive function and body weight of the patient was restored, and he remains free from depression," reports Kazutoyo Inanaga, MD, PhD. Inanaga reports that Amyloban 3399, made by Mushroom Wisdom Ltd. (New Jersey, US), also aided recovery in 10 patients with treatment-resistant schizophrenia.

Amycenone's antidepressant effect stems, at least partly, from the compound's ability to quell inflammation, according to a 2015 Japanese study led by Wei Yao. The authors state, "Inflammation ... plays a role in the pathophysiology of depression and some anti-inflammatory drugs have antidepressant-like effects." People with depression tend to have higher serum levels of TNF-α, a pro-inflammatory cytokine. Moreover, postmortem brain tissue samples from 14 people with a major depression showed elevated gene expression of pro-inflammatory cytokines compared with 14 controls. The tissue samples in this 2011 study were taken from a brain region associated with reward-related behavior.

Wei Yao and colleagues looked at the effect of amycenone on inflammation levels and depressive behavior in mice injected with bacterial endotoxin lipopolysaccharide (LPS). LPS is known to cause pro-inflammatory cytokine signaling in rodents followed by depressionlike behavior, peaking 24 hours after injection. Sixty minutes before receiving the LPS injection, mice were given an oral dose of amycenone dissolved in a vehicle (0.5% carbomethoxycellulose), an oral dose of the vehicle alone (inactive control), or paroxetine hydrochloride (Paxil) dissolved in distilled water (active control).

The researchers found that pretreatment with amycenone (200 mg/kg) lessened the LPS-induced TNF-α increase to about the same level that paroxetine did. Lower doses of amycenone (50 or 100 mg/kg), in comparison with the vehicle control, also had an effect on TNF-α levels but not as strong as the higher dose. High-dose amycenone (200 mg/kg) pretreatment also significantly increased anti-inflammatory cytokine IL-10 blood levels, but not as high as paroxetine. The difference in IL-10 levels, however, did not produce a marked difference in the rodents' behavior. Amycenone (200 mg/kg) significantly lessened rodents' immobility time (signifying depression) during a tail suspension test and a forced swimming test, compared with the vehicle control. The amycenone responses were similar to those displayed by the paroxetine-treated group. Neither amycenone nor paroxetine produced an effect on mice that were not treated with LPS.

Lion's mane has a long and safe history as a food and as a medicinal in traditional Chinese medicine. Wei Yao and colleagues say that the extract amycenone, unlike SSRIs and other pharmaceutical antidepressants, has no adverse effects. They conclude, "It is, therefore, likely

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that amycenone may be [a sole] supplement to prevent inflammation-induced depression."

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Brain Injury and Retinal Pathways

Traumatic brain injury often produces largely unrecognized visual and nonvisual retinal signal processing dysfunctions. These dysfunctions can disrupt spatial orientation and motor control and produce numerous physical and emotional symptoms, says neuro-optometrist Deborah G. Zelinsky. Neuro-optometrists primarily focus on the involuntary and unconscious eye movements that are a normal part of ambient processing that contributes to a person's spatial orientation. Through the use of specialized eyeglasses, neuro-optometrists can change the way that light angles onto the retina and thereby help patients adapt to environmental signals beneath their conscious awareness.

In her 2010 article, Zelinsky gives examples of brain injury complaints that can be relieved with special lenses, prisms, and filters. For example, reading comprehension problems that arise after a mild brain injury may be due to disrupted visual processing that affects eye movement. Eyeglasses that angle light differently help steady ambient processing, allowing eye movement to follow written text more smoothly. Also, dizziness that does not respond to gaze stabilization techniques can be caused by too much light stimulation on a hypersensitive point in the retina. A partial occlusion filter can reduce the stimulation and relieve the dizziness. Sometimes, patients perceive objects as being farther away with one eye than with the other, a condition that causes nonconscious compensatory head rotation and leads to neck and back pain. Eyeglasses that angle light from the side can solve the problem. If patients complain that prescription eyeglasses for 20/20 vision give them headaches, Zelinsky makes a small prescription change to slightly blur central eyesight, "allowing better comfort and more stable ambient processing," until patients can accept the sharper prescription. Retinal processing dysfunctions can also cause fatigue, sleep disturbances, and difficulty with auditory processing.

"By the use of lens prescriptions, filters, tints, prisms, and other techniques, the neuro-optometrist can remediate or compensate for many visual and sensory misperceptions, freeing the patient's cognitive reserves for the important work of other rehabilitation professionals," writes Zelinsky.

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Reversing Cognitive Decline

A multifaceted protocol is successfully reversing cognitive impairment and early Alzheimer's disease, according to neuroscientist Dale E. Bredesen at UCLA's Mary S. Easton Center for Alzheimer's Disease Research. In a 2014 report, Bredesen describes results from the first 10 patients to use a personalized metabolic enhancement program designed to optimize biochemistry related to neuroplasticity. Individualized protocols, based on patient history and laboratory tests, address multiple factors including glucose metabolism, hormone levels, inflammation, cellular activity, ApoE genetic status, nutrition, stress, and sleep quality. Shifting metabolic function toward optimal levels can reverse several chronic illnesses including diabetes, osteoporosis, and cardiovascular disease. The same is true for cognitive decline, says Bredesen.

Treatment primarily consists of lifestyle changes, herbs, and nutritional supplements. Numerous supplements are used to improve sleep quality, reduce homocysteine levels, optimize mitochondrial function, and enhance cognitive function. Supplemental hormones (e.g., estradiol, progesterone, pregnenolone, thyroid) and chelation to remove heavy metals are also used as needed. Diet, regular exercise (30–60 minutes, 4–6 times/week), and 8 hours of good-quality sleep are key for reversing neurodegeneration. Diet recommendations include eliminating processed foods and simple carbohydrates and following a low-glycemic, low-grain diet plan. A high-glycemic diet contributes to inflammation and insulin resistance – both of which are factors in cognitive decline. In addition to the diet plan, Bredesen and colleagues recommend fasting for 12 hours each night, including 3 hours before bedtime, to reduce insulin and amyloid-β levels. Bredesen says, "Even though it is not expected that most patients will be able to follow every single step of the protocol, as long as enough steps are followed to exceed the threshold [of neurodegeneration], that should be sufficient."

Bredesen's 2014 article contains the rationale for this therapeutic program, results from long-term observation of the first 10 patients and 3 case studies. The 10 patients had memory loss related to Alzheimer's disease, amnestic mild cognitive impairment, or subjective cognitive impairment. Six of them had stopped working or were having difficulty performing their jobs because of cognitive decline. Only 1 of the 10 – a person with "very late stage" Alzheimer's – *did* not improve. The others showed cognitive improvement within 3 to 6 months of starting the program. Those who had quit their jobs or were struggling to continue were able to return to work with improved performance. Improvement was sustained as long as the patients continued to follow the program – up to 2½ years as of 2014.

"It is noteworthy that the major side effect of this therapeutic system is improved health and optimal BMI (body mass index), a result in stark contrast to monopharmaceutical treatments," writes Bredesen. "However, the program is not easy to follow, and none of the patients followed the entire protocol." Patients complained about the diet and lifestyle changes and number of supplements, but they were motivated by impending cognitive loss. While this anecdotal evidence shows that a multifaceted program can reverse cognitive decline in some people, larger trials are needed to determine its effectiveness in a larger population with later stages of cognitive decline and familial Alzheimer's. In the meantime, this program does no harm and offers the possibility of benefit for people facing an otherwise irreversible condition.

Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. *Aging (Albany, NY)*. September 2014;6(9):707–717. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4221920. Accessed July 23, 2015.

Wellness Recovery Action Planning (WRAP)

Wellness Recovery Action Planning (WRAP) for people with mental illness reduces psychiatric symptoms and increases hopefulness and quality of life, according to a 2011 study. This illness self-management program is conducted by peers who are in stable recovery from mental illness. The curriculum, which is presented during 8 to 12 weekly sessions, gives participants tools for developing a daily maintenance plan for enhancing their own mental health. By February 2011, Copeland Center for Wellness and Recovery (Chandler, Arizona) had trained over 2000 WRAP group facilitators and 150 Advanced Level Facilitators, who are qualified to train others.

The 2011 study, led by Judith A. Cook, involved 519 adults with schizophrenia, schizoaffective disorder, bipolar disorder, or a depressive disorder. All participants were recruited from publicly funded outpatient community health delivery settings in six Ohio communities. Patients were randomly assigned to a WRAP program (eight 2.5-hour weekly sessions) or a wait-list control. Psychiatric symptom severity, hopefulness, and quality of life were measured using validated self-report assessment tools during interviews conducted by blinded researchers. The interviews took place 6 weeks before WRAP sessions began, 6 weeks after WRAP ended, and 6 months after the second assessment.

Symptom presence and severity in the WRAP cohort were significantly reduced compared with controls at posttreatment assessment. Patients in both groups reported further improvement at the 6-month follow-up. Compared with the control, WRAP patients' hopefulness scores improved significantly over time. At the 6-month follow-up, quality-of-life measures were higher in the WRAP cohort than in the control. The authors report, "The greater the number of WRAP sessions attended, the more participants' outcomes improved."

WRAP is not the only clinically tested mental health program to use peer support. A 2014 review article found 20 studies in which peers were used in three types of programs: peers facilitating structured curricula (e.g., WRAP), peer support in addition to traditional care, and peers in regular provider roles. Programs involving peer facilitators and peer support have shown several benefits including more patient engagement, better patient–provider relationship, and less need for inpatient care. Also, patients in these programs reported greater empowerment and hope for recovery. The effectiveness of peers' serving as traditional providers has been less clear.

The reviewers point out that it's impossible to say how much of the positive results of WRAP and similar peer-led programs is due to the curricula and how much is simply from being peer led. They suggest conducting studies in which curricula are conducted by paraprofessionals without a history of mental illness.

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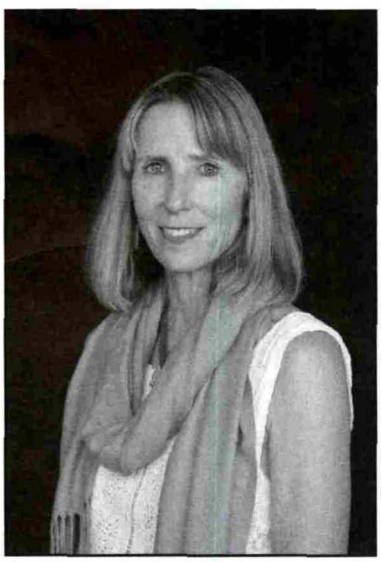
Pathways to Healing

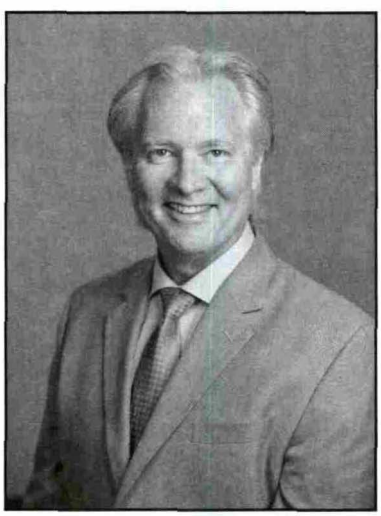
by Elaine Zablocki

Functional Medicine Poised for Growth

Over the past 15 years, the Institute for Functional Medicine (IFM) has evolved from an innovative organization on the outskirts of US medicine to a well-respected organization whose ideas are tested and adopted in mainstream settings. IFM is currently experiencing significant growth, with conference attendance growing at a rate of over 20% per year, and most conferences selling out. The majority of new attendees choose to enter IFM's certification program to continue their education.



Laurie Hofmann



Patrick Hanaway, MD

In the past, IFM attracted clinicians who were coping with chronic conditions that didn't respond to the usual paradigms of modern medicine. "Typically, people came to us saying, 'This isn't working; is there something else out there that can work?' They came with a hope and a dream that there might be something else," said Patrick Hanaway, MD, IFM chief medical education officer. "Today we see many journal articles incorporating much greater awareness of functional medicine. Nowadays people come to us saying, 'I need a tool set to help me deal with patients with complex chronic disease. Teach me how to do this.'"

Over the past few years, IFM has codified the functional medicine approach into a specific series of steps, an operating system, "and that's a huge milestone," Hanaway said. "We teach people how to meet with their patients. We focus on the elements that have always been a part of the functional medicine approach, but now we do it in a more structured manner so we can understand what is the root cause and what is the leverage point."

The clinician listens to the patient's story, noting particularly:

- antecedents: factors that predispose an individual to an illness or pattern;
- triggers: factors that provoke the symptoms and signs of illness; and
- mediators: factors (biochemical or psychosocial) that contribute to pathological changes and dysfunctional responses.

Functional medicine thinks in terms of seven fundamental organizing systems of the human body:

assimilation	defense and repair
energy	biotransformation and elimination
communication	transport
structural integrity	

The functional medicine practitioner takes time to listen to the patient's narrative, their story of how they are functioning, from their viewpoint. An initial intake interview may take 60 to 90 minutes. At the same time, clinicians aren't drowning in a mass of information. They note the factors that tend to initiate and perpetuate disease, and frame the narrative in relation to imbalances that frequently occur in the fundamental organizing systems. They listen in an organized way, taking a stepwise approach that leads to a range of suggestions to help patients remove the root cause(s) of their problems.

Recently, IFM increased its emphasis on the ways that clinicians prepare for this interaction with patients. "Really hearing the patient's story is so important," Hanaway said. "When we look at people who are effective as healers, we see they have openness and curiosity. They don't start out with an attitude of 'I know what's going on and I know what needs to happen.' In order to support behavior change and the healing process, I need to be fully present. As a practitioner, if I'm having a bad day, I need to find ways to gather myself and leave all that behind, so when I'm engaging with the patient, I'm engaging with my heart and mind open."

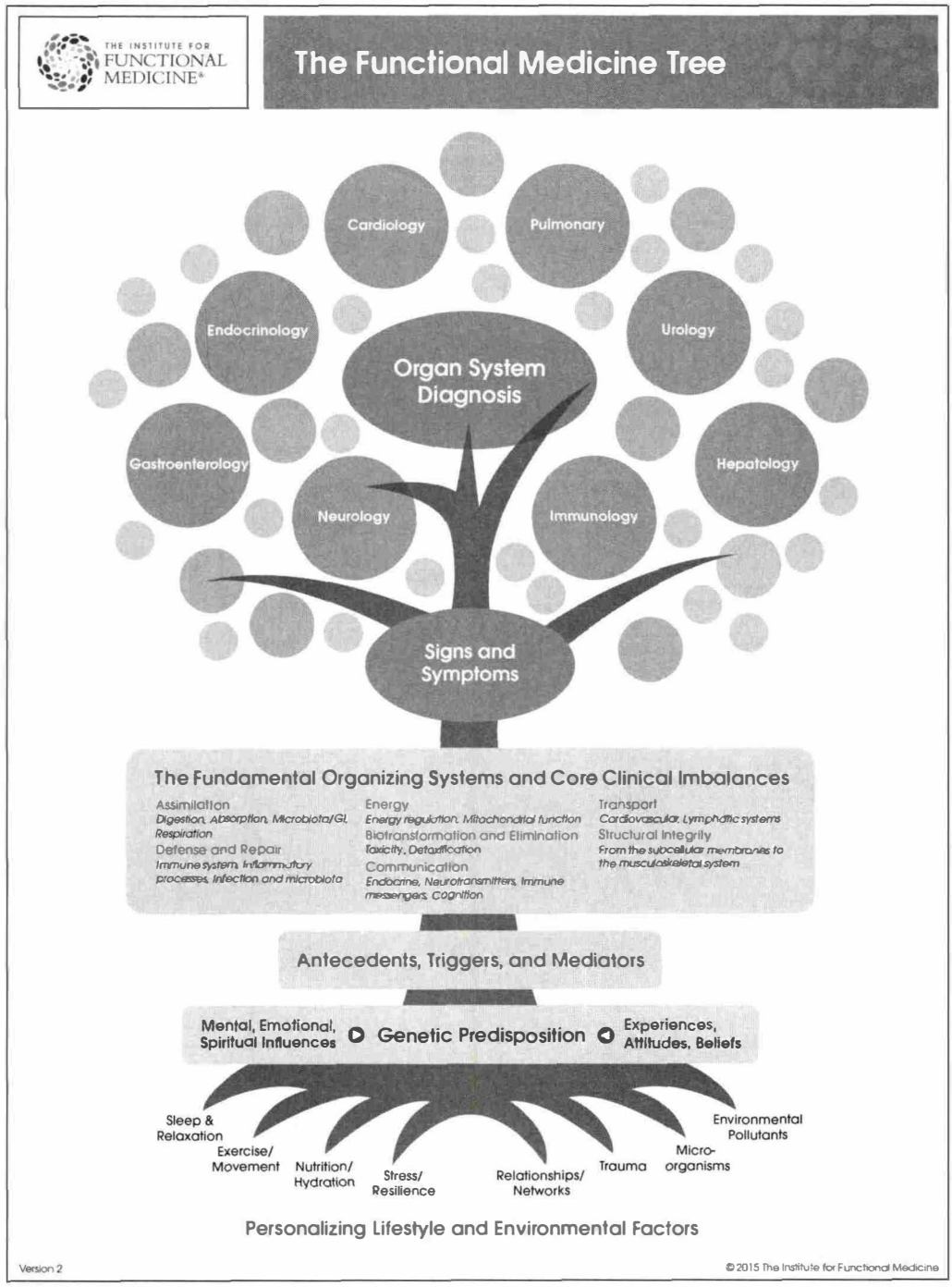
Educational Path for Functional Medicine Practitioners

The IFM website offers introductory e-learning courses at no charge, including "A Systems Approach to Reversing the Epidemic of Chronic Disease" and "Introduction to Functional Nutrition: Clinical Solutions for Addressing the Underlying Causes of Disease." IFM's foundational course, "Applying Functional Medicine in Clinical Practice (AFMCP)," is a 5-day on-site program designed to help practitioners deepen their clinical understanding and practical application of the functional medicine matrix. The course is based on small-group, interactive, case-based learning led by IFM faculty and certified practitioners. Participants receive a clinical practice toolkit that includes documents such as intake forms, food diaries, assessment questionnaires, patient handouts, and activity/exercise and comprehensive dietary plans.

"AFMCP teaches the foundation and framework of functional medicine, as well as many practical tools," Hanaway said. "Afterwards we encourage participants to go back to their practices and start using these tools. We have forms online so practitioners can ask specific questions and receive responses from our MedEd team and faculty. That's all part of our ongoing training for individuals."

After the foundational course, six 2½-day advanced practice modules are available, each focused on an area of potential clinical imbalance: gastrointestinal, inflammation, detoxification, hormonal, cardiometabolic, and energy production. Some practitioners choose programs depending on their personal schedule and interests. Others follow the more formal path to becoming an IFM Certified Practitioner. This means completing AFMCP, all six advanced practice modules, presenting a case study based on an IFM-provided template, and passing a written exam. At present, 327 people have been certified since fall 2013, and another 850 are moving forward with the process.

About half to two-thirds of the people who currently attend IFM courses are MDs and DOs. Others who participate include chiropractors, naturopathic physicians, advance practice nurses, and physician assistants. "Probably nutritionists are the second biggest group we attract right now," said Hanaway. "They find this to be an important construct in terms of placing diet within a context and learning how to use different diets therapeutically for different people. Nutrition is critical in treating and preventing chronic disease."



Pathways to Healing

Preparing for Growth

IFM currently offers training courses throughout the US and in international locations that include China, the UK, and South Africa. Nearly 5000 practitioners have taken AFMCP over the last 19 years, and demand has grown so much that attendance is expected to exceed 1000 practitioners in 2016.

Over the past year, IFM has shifted to an increased focus on an adult-based learning approach, which means fewer lectures and more hands-on education. Participants focus on specific cases, working in pairs or small groups. Facilitators circulate, helping each group to ask themselves, how do we actually do this? Have we considered all the factors? What could we do next? "Instead of being passive listeners, not really engaging the material, they become actively engaged and committed to the learning process," Hanaway said. "How do we become a true educational organization? It's not just about content; it's also about how we act as teachers and listen to learners."

In addition, IFM is beginning to live-stream courses in order to accommodate more learners and respond to growing international interest. "We're considering various platforms to be able to offer this education internationally," Hanaway said. "We hope to find ways to combine interactive principles of adult learning with the live-streaming experience, and possibly with local facilitation."

Laurie Hofmann, IFM's CEO, articulates bold goals for the future. "IFM's mission is to ensure the widespread adoption of functional medicine as the standard of care," she said. "The chronic disease epidemic, which is now global in scope, threatens to bankrupt national economies if current trends continue. Something has to change. Functional medicine offers a highly sophisticated operating system, tools, and training program to equip health-care practitioners from all disciplines to take on this daunting challenge and succeed."

Resources

The Institute for Functional Medicine
https://www.functionalmedicine.org
https://www.functionalmedicine.org/getstarted/resources/IFMTools

Free Educational Online Modules
https://www.functionalmedicine.org/getstarted/free

White Paper
21st Century Medicine: A New Model for Medical Education and Practice
http://www.marthaherbert.org/library/IFM-White-paper-21stCenturyMedicine.pdf

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

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Health Risks & Environmental Issues

by Rose Marie Williams, MA
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Lice and Fukushima Updates

Lice

This column reported on the perils of lindane use on head lice in April 2000. Lindane, an organochlorine pesticide, is closely related to DDT. Its toxicity has been considered carcinogenic and neurotoxic, and it is associated with birth defects, kidney damage, endocrine disruption, breast cancer risk, and more. Lice have been developing a resistance to lindane, while children have not. Dr. Marion Moses, author of *Designer Poisons,* believes that "lindane should be banned," and "not allowed for any use whatsoever."[1]

Permethrin, like other pyrethroids, which are synthetic versions of pyrethrum pesticides derived from the chrysanthemum plant family, do not break down as easily. Permethrin is another chemical toxin found in over-the-counter and prescription lice-treatment shampoos. Its safety is also questionable. Risk factors include asthma, anaphylactic shock, pneumonia, vomiting, diarrhea, irritability to sound and touch, convulsions, stinging, burning, itching, numbness, decrease in blood pressure, and death. Moses even tells of brain and nervous system damage resulting in death in infants and children after exposure to permethrin products. A toxic synergist, piperonyl butoxide, is an additional ingredient and has been found to cause cancer and birth defects in rats. Again, Moses warns, "We cannot recommend it for use on children."[1]

None of these toxic risks seem to apply to the very pests that they are intended to control – lice. Quite the opposite has happened. Scientists have found that a whopping 99.6% of lice in the US have developed resistance to over-the-counter and prescription shampoos containing permethrin. *Pesticides and You* (www.beyondpesiticdes.org) reported on a recent study "on lice resistance published in the *Journal of the Entomological Society of America* indicating hazardous chemical treatments not only are not necessary given effective least-toxic alternatives, but also are not able to provide the lice control that manufacturers claim."[2]

The report indicates that the UK and Europe no longer use pyrethroids. "Virtually everyone except the United States and Canada have given up using these over-the-counter products," claims John Clark, PhD, a professor of environmental toxicology and chemistry at the University of Massachusetts Amherst and coauthor of the study.[2]

Eric Ayers, MD, with the Children's Hospital of Michigan, reported in the *Detroit Free Press* "that lice not killed by chemical treatment not only survive, but become stronger." Other findings indicate that the more a product is used within a community, the more lice in that community become resistant, according to Shirley Gordon, PhD, director of the Head Lice Project at Florida Atlantic University. "We don't like to use the term super lice, because it's sensational and frightening. It's not a superbug, but a louse that has become resistant."[2]

The US Environmental Protection Agency (EPA) considers permethrin part of the synthetic pyrethroid class of chemicals, "likely to be carcinogenic" when used in lice shampoo. Unfortunately, for American consumers, the chemical is regulated by the Food and Drug Administration (FDA), which allows its use on infants over 2 months old.[2] For those folks who might disagree with the FDA's decision to allow such poisons to be used on babies and children, or even adults for that matter, there are alternative, nontoxic treatments.

Safer Treatments

Lice have made major comeback in schools; therefore, it is imperative to remain vigilant and proactive. Using a magnifying glass every so often to check for little grayish white eggs (nits) attached to the hair shaft is a first step.

Moses suggests using a soap shampoo, or any shampoo *except* a *lice shampoo.* Her recommendation is to

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thoroughly shampoo, making sure to cover all areas of the scalp and hair. Rinse completely, and shampoo again. This time do not rinse. Wrap a towel around the head for a few minutes, then begin combing with a special fine-tooth comb designed to remove dead lice and nits. Lice have not developed a resistance to this old-fashioned technique. Specially designed combs can be purchased from a pharmacy or by mail order.[1]

Coconut-oil- or olive-oil-based shampoos and soaps, or simply pure coconut or olive oil, are considered very effective treatments for killing adult lice but may not be as effective at killing or removing the nits. Using the lice comb is a good follow-up. Both oils are safe. Instead of poisoning, the oils kill the active lice by smothering them. An added bonus is that the oil treatment makes nit removal easier.[1]

Tea tree oil is safe and effective. It should be put directly on the scalp and left on for about 10 minutes. About 20 drops can be added to a half-bottle of shampoo and used in the child's regular hair washings for a week or two as a follow-up measure.[1]

Essential oils are wonderful aromatic gifts of nature with healing qualities. For lice treatment, Dr. Andrew Weil suggests an herbal remedy consisting of 2 oz of vegetable oil, 20 drops of tea tree oil, and 10 drops each of the following essential oils: rosemary, lavender, and lemon. Weil advises first doing a skin sensitivity test by applying a few drops of the mixture to the inside of the elbow and waiting a few hours to observe if there is any irritation. To treat for lice, apply mixture to infected head, wrap in towel for 1 hour, then shampoo. Repeat at least one more time later in the week to get rid of the next batch of hatched lice.[1]

Several nontoxic products are available for purchase in health food stores or by mail order. Hair Clean 1-2-3, developed in Israel, is available in many health food stores. "One dermatologist in Key West told her colleagues the lice were running off the heads like clowns out of a Volkswagen." Lice R Gone is a nontoxic lice shampoo treatment that removes lice and nits on contact. It is a natural enzymatic formula that is pesticide free, environmentally friendly, and safe for children.

The Winter 2014/2015 issue of *Pesticides and You* replied to a mother's inquiry about lice control, offering several suggestions including desiccation, or heat control as being the most effective nontoxic means of killing the nits. Many hair salons now offer this service. Do-it-yourself at home hair dryers were not recommended because lice can become airborne and spread to others. Beyond Pesticides offers a fact sheet: "Getting Nit Picky About Head Lice."[3]

The American Head Lice Information Center has an entertaining award-winning video (www.headliceinfo.com).[1]

For additional information on this topic, and to report any findings of head lice to assist in tracking annual outbreaks, please contact National Pediculosis Association (NPA) www.headlice.org.

Fukushima

The ongoing radioactive pollution from Japan's Fukushima Daiichi nuclear plant disaster of March 2011 was reported in the October 2013 *Townsend Letter*. The accident, caused by an offshore earthquake and tsunami waves over 130 feet, caused major irreparable damage to the nuclear facility. The subsequent leaking of radioactive contaminated water and air pollution around the globe is possibly the worst environmental disaster of modern times, even though there is little news coming from Japan these days.[4]

Immediately following the accident, workers tried unsuccessfully to contain highly radioactive wastewater. This problem was compounded by groundwater pouring uncontrollably into the plant's ravaged reactor buildings, where it became highly contaminated. The temporary solution was to siphon the water into huge storage tanks, but there were not enough tanks to hold all the strontium-laced water at the plant. Further efforts to contain the water in specially constructed pits proved worthless when the pits began to leak.[4]

Three major aftershocks hit northeast Japan in the months following the initial disaster of March 2011. On July 29, 2012, a 6.4 magnitude aftershock quake hit the area. On December 7, 2012, the region was hit again with an aftershock of 7.3 that shook buildings and caused 3 foot tsunami waves, forcing an evacuation of 26,000 people. February 2013, one year after the major crisis, another quake measuring 6.9 did not cause a tsunami but sent waves of fear across the same region that was hit by the 9.0 earthquake that left 20,000 dead or missing.

Problems at the Fukushima disaster site are ongoing, constantly changing, and degrading environmental and human health around the globe. Some problems listed by *Nukewatch Quarterly* are as follows:

- August 2014: Tokyo Electric Power Co. (TEPCO) admitted that all the uranium fuel in Reactor 3 melted and burned into the bottom of the reactor's cement containment vessel, going 2 feet into the concrete. "So harrowing is the problem of removing this mass of hot, molten fuel wreckage, that Tepco has said it won't begin the attempt for seven years."
- Billions in subsidies being offered to Japanese communities to store radioactive contaminated soil and debris are described as "bribes" by Greenpeace.

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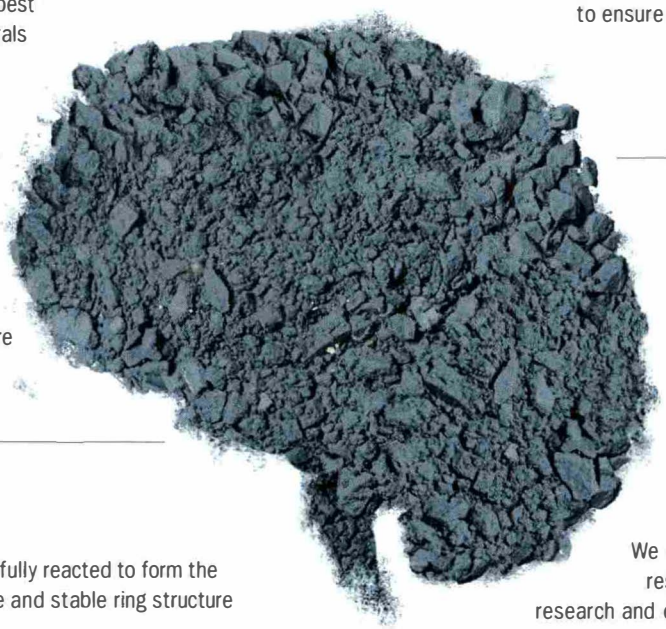

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- An October 2014 typhoon caused the amount of tritium, radioactive hydrogen, and strontium-90 in groundwater to jump 10-fold due to heavy rain, causing great concern among the population about food contamination and lax government regulations.
- October 29, 2014: Radioactive soil stored at schools cannot be transferred to other locations because of a legal technicality. Burning thousands of tons of contaminated soil in municipal incinerators created immediate problems dealing with radioactive ash, which has increased contamination levels in many communities.
- November 11, 2014: The Oregon *Statesman Journal* reported that cesium-134 found in seawater from Fukushima had reached the California coast.[5]
- March 2015: Hong Kong finds traces of radioactive cesium-137 in tea and vegetables imported from Japan. "Ingestion of even the smallest traces of radioactive materials can cause cancer and other illnesses," which "may not appear for years or decades following ingestion or inhalation."[6]
- May 5, 2015: Taiwan imposed new bans on food imports from Japan due to faked labels that disguised the products which were really from contaminated areas in Japan, reported the French news agency AFP.[6]

Other reminders of nuclear disasters include the March 1979 near meltdown of the nuclear facility at Three Mile Island near Harrisburg, Pennsylvania, due to mechanical failure and poor decisions. Less than a decade later, the world was shocked by the April 26, 1986, explosion and subsequent meltdown of the Chernobyl nuclear facility in Ukraine, which caused thousands of deaths and ongoing cancers.

What do these three nuclear disasters have in common? A lot, according to *Nukewatch Quarterly* editor Arianne Peterson. She indicates that all three catastrophes occurred in spring: Three Mile Island, March 28, 1979; Chernobyl, April 26, 1986; and Fukushima, March 11, 2011. More striking yet is the similarity of events leading up to each accident and human failures that exacerbated each catastrophe.[7]

Peterson cites an article by Edward M. Geist in the April 2014 *Bulletin of the Atomic Scientist,* wherein he describes how government authorities realized "to their horror their existing plans were too vague to address the challenges now facing them," while technical experts disagreed "about what to do next." "Some ... asserted events were 'under control,' while others warned of ongoing radioactive emissions" could lead to "an eminent release of catastrophic proportions." Worse yet, "no one could predict the likelihood or timing of such a development confidently enough to inform decisions about ordering evacuations," or would this "only incite unnecessary panic?" "This narrative played out exactly the same three separate times over the past thirty-six years."[7]

Think globally – act locally. Get active. Join an antinuke organization, or at least support one with a donation (nukewatch.org, NRDC.org, ucsusa.org, psr.org, greenpeace.org). Write, call, e-mail your elected officials protesting the presence of a nuclear facility near you. Promote safer energy alternatives such as solar and wind. Become part of the growing trend of home and business owners who are installing solar power. Vote with your dollar. It is often more powerful than the voting booth.

Just I was about to send in this column, I received the latest copy of *Earthwise* (Summer 2015) from the Union of Concerned Scientists, with inspiring information about bipartisan support for renewable energy in what are generally considered red (Republican) states. North Carolina is now second in the country, having installed more solar photovoltaic systems than any other state except California. Even Apple is jumping on the solar bandwagon by developing a 200-acre solar farm in the western part of the state to power its new iCloud data center. Oklahoma now ranks second in the nation for wind power installations in 2014 and fourth for total electricity generated from wind. The American Wind Energy Association indicates that there is cost savings of wind over natural gas. Texas may be replacing oil rigs with windmills. Texas installed more wind turbines than any other state in 2014, now accounting for 10% of its electricity.[8]

Notes

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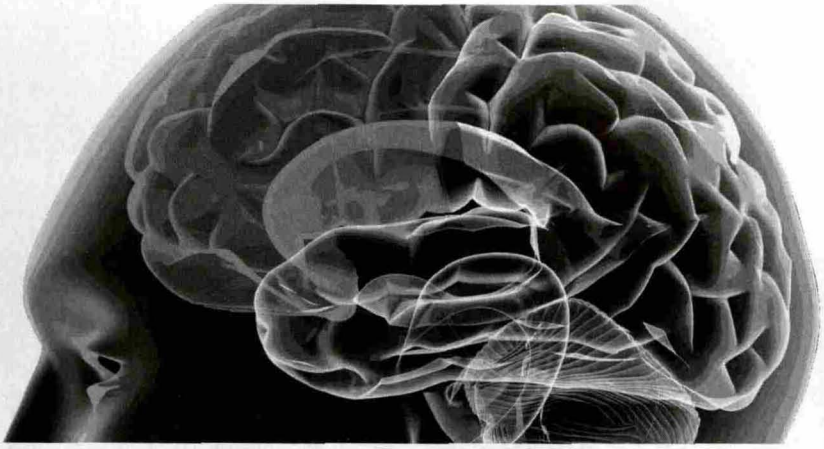


The Dementia-PRP Connection

As the most common form of dementia, Alzheimer's disease (AD) places an overwhelming burden on families, societies, and economies; approximately 1 in 9 people over the age of 65 have AD. New research suggests that at age 65, women have a 1 in 6 chance of developing AD, whereas men have a 1 in 11 chance, and dementia in women tends to develop faster than in men. AD is now appearing in people in their forties who exhibit symptoms of non-memory cognitive impairments, such as deficits in language and judgement. The epidemic of AD and early-onset AD correlates with the increasing prevalence of Leaky Gut Syndrome (LGS), and leaky gut equals leaky brain. The critical first step in turning the tide on this horrifying epidemic is healing the leaky gut. Colostrum-LD® is the only medicinal food containing the bioactive components clinically proven to heal and prevent LGS. Moreover, Colostrum-LD® contains Proline-Rich Polypeptides (PRPs) which show promise in patients with mild to moderate cognitive dysfunction.

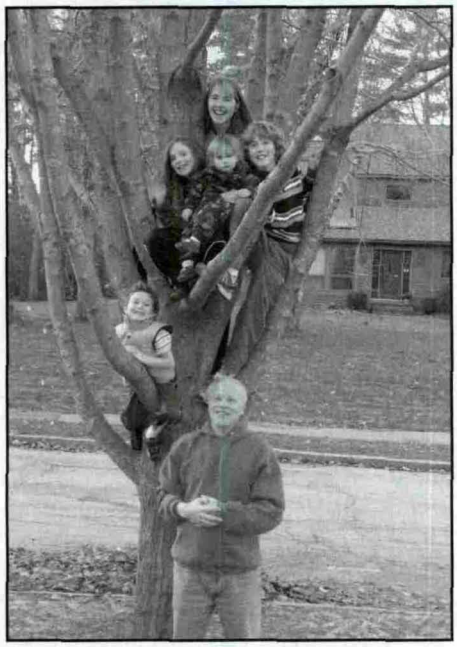
A Novel Approach to Dementia Treatment

PRPs, also termed *colostrinin*, in colostrum enhance the defense against oxidative stress, prevent beta-amyloid aggregation, and decrease expression of inflammatory chemokines and cytokines, thereby attenuating inflammatory processes that precede AD. PRPs are likely the most promising treatment identified to date. Research has shown that PRPs improve the mental functioning of Alzheimer's patients with mild to moderate dementia. PRPs, specifically PRP-3s, inhibit the initiation of inappropriate inflammatory cascades associated with autoimmune responses and help stop the destruction of body tissue and organs. PRPs are not species specific, which makes bovine colostrum an excellent and abundant source. Concentrated PRP-3s, such as those in IRM Immune Response Modulator®, have a valuable role in the early stages of cognitive decline.

Other components of bovine colostrum play a role in mitigating age-related depression, cognitive decline, and dementia. Serotonin levels often decline with age, and lower tryptophan levels affect the brain's ability to synthesize sufficient serotonin. Chronic stress, believed to be a contributing factor for low brain serotonin levels, has been associated with poor memory performance. Increasing dietary intake of tryptophan relieves depression and stress in people highly vulnerable to stress. Alpha-lactalbumin increases the plasma ratio of tryptophan which in turn, increases brain serotonin activity, reduces cortisol concentration, improves coping ability, and improves mood under stress. Studies show that alpha-lactalbumin significantly improved memory test performance in stress-compromised individuals. Bovine colostrum is a natural source of tryptophan and alpha-lactalbumin.

In the absence of an efficacious and cost-effective treatment for neurodegenerative diseases, Colostrum-LD and IRM are viable alternatives. The prospect of delaying the onset and even reversing the disease process is good news for patients and their families. For maximum results, daily use of Colostrum-LD and IRM is recommended by physicians and healthcare providers. Both Colostrum-LD and IRM are sourced from the highest quality bovine colostrum collected year-round from pasture-fed, antibiotic-free and hormone-free cows living in the Southwest United States.

For more information, visit Colostrum Therapy.com (for professionals) or CenterforNutritionalResearch.org (for consumers).



Literature Review & Commentary

by Alan R. Gaby, MD
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Melatonin for Alzheimer's Disease

Eighty patients (mean age, 75.3 years) with mild-to-moderate Alzheimer's disease who were receiving standard therapy (acetylcholinesterase inhibitors with or without memantine) were randomly assigned to receive, in double-blind fashion, 2 mg of prolonged-release melatonin or placebo each night for 24 weeks. Compared with placebo, melatonin significantly improved cognitive performance, as measured by the Instrumental Activities of Daily Living score ($p = 0.004$) and the Mini-Mental State Examination score ($p < 0.05$). Sleep efficiency, as measured by the Pittsburgh Sleep Quality Index, component 4, was also better with melatonin than with placebo ($p < 0.02$). The beneficial effect of melatonin on cognitive function appeared to be more pronounced in patients with insomnia than in those without insomnia.

Comment: Melatonin promotes normal sleep. Because melatonin levels are reduced in patients with Alzheimer's disease, supplementation with this hormone might be beneficial. The results of the present study demonstrate that melatonin, as compared with placebo, improved both cognitive function and sleep efficiency in patients with Alzheimer's disease. The beneficial effect of melatonin on cognitive function could simply be due to promoting better sleep, although other mechanisms might be involved as well.

Wade AG et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. *Clin Interv Aging*. 2014;9:947–961.

Acetyl-L-Carnitine for Dysthymia in the Elderly

Eighty elderly patients (mean age, 72 years) with dysthymic disorder were randomly assigned to receive, in double-blind fashion, acetyl-L-carnitine at a dose of 1 g 3 times per day or 20 mg per day of fluoxetine (a selective serotonin-reuptake inhibitor) for 6 weeks. Significant improvements were seen in both groups on the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, and the Beck Depression Inventory. The degree of improvement in the 2 groups was similar.

Comment: Dysthymic disorder (also called dysthymia) is characterized by a depressed mood that does not fit the diagnostic criteria for major or minor depression. Criteria for diagnosing dysthymic disorder include the presence of a depressed mood for most of the day, for more than 50% of days, for at least 2 years. In children and adolescents, the mood can be irritable and the duration must be at least 1 year. At least 2 of the following symptoms are also present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, difficulty concentrating or making decisions, and feelings of hopelessness. There is considerable overlap between dysthymic disorder and major and minor depression. The cause of dysthymic disorder is not clear, but it appears to involve abnormalities of serotonergic and noradrenergic systems. The results of the present study indicate that acetyl-L-carnitine is as effective as fluoxetine in the treatment of dysthymic disorder in elderly patients. Although its mechanism of action is not fully understood, acetyl-L-carnitine is known to function as a neurotransmitter.

Bersani G et al. L-Acetylcarnitine in dysthymic disorder in elderly patients: a double-blind, multicenter, controlled randomized study vs. fluoxetine. *Eur Neuropsychopharmacol*. 2013;23:1219–1225.

Ginkgo Biloba for Age-Related Cognitive Decline

One hundred sixty patients with mild cognitive impairment (defined as a score of at least 6 on the 12-item Neuropsychiatric Inventory [NPI]) were randomly assigned to receive, in double-blind fashion, 240 mg per day of *Ginkgo biloba* extract EGb 761 (ginkgo) or placebo for 24 weeks. The mean NPI score decreased (improved) to a significantly greater extent in the ginkgo group than in the placebo group (-7.0 vs. -5.5; $p = 0.001$ for the difference in the change between groups). The proportion of patients

who had a clinically relevant improvement (a reduction of at least 4 points in the NPI score) was significantly greater in the ginkgo group than in the placebo group (78.8% vs. 55.7%; p = 0.002). The treatment was well tolerated.

Comment: The results of this study support previous research demonstrating that ginkgo can improve cognitive function or slow the rate of cognitive decline in people with age-related cognitive impairment. The use of ginkgo for this purpose has become somewhat controversial in recent years, because of several studies showing that it does not prevent the development of dementia in elderly people with initially normal cognitive function. However, studies of people who already have aged-related cognitive impairment or early dementia have shown consistently positive results.

Gavrilova SI et al. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *Int J Geriatr Psychiatry*. 2014;29:1087–1095.

B Vitamins Enhance Response to Antidepressants

One hundred fifty-three patients aged 50 years or older (mean age, 63 years) with major depression who were being treated with citalopram (a selective serotonin-reuptake inhibitor) were randomly assigned to receive, in double-blind fashion, placebo or daily B vitamins (2 mg of folic acid, 25 mg of vitamin B6, and 500 μg of vitamin B12) for 1 year. Symptom severity was measured by the Montgomery-Åsberg Depression Rating Scale. The remission rate was similar between groups at 12 weeks (vitamins, 79.4%; placebo, 78.1%), but was higher in the vitamin group than in the placebo group at 26 weeks (85.3% vs. 76.5%) and 52 weeks (85.5% vs. 75.8%). In post hoc analysis, the odds ratio for remission among patients with baseline plasma homocysteine levels above the median (greater than 10.4 μmol/L) was 3.47 (95% confidence interval, 1.22–9.84). However, among patients with baseline homocysteine levels below the median, the remission rate did not differ significantly between groups.

Comment: High plasma homocysteine levels have been associated with depression. Supplementation with folic acid, vitamin B6, and vitamin B12 is known to lower homocysteine levels. Some studies have shown that each of these vitamins can improve depression in certain clinical circumstances. In the present study, supplementation with folic acid, vitamin B6, and vitamin B12 enhanced the response to antidepressant medication in middle-aged and elderly adults with high plasma homocysteine levels.

Almeida OP et al. B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial. *Br J Psychiatry*. 2014;205:450–457.

N-Acetylcysteine for Autistic Children

Fifty children (aged 4–12 years) with autistic disorders were randomly assigned to receive, in double-blind fashion, N-acetylcysteine (NAC) or placebo for 10 weeks. The

dosage was 200 mg 3 times per day for children weighing less than 20 kg, and 300 mg 3 times per day for children weighing 20 kg or more. All children were treated with risperidone. Forty patients completed the trial. Compared with placebo, NAC resulted in significant improvements in the Aberrant Behavior Checklist-Community irritability ($p = 0.01$) and hyperactivity/noncompliance ($p = 0.02$) subscales.

Comment: An imbalance in the excitatory/inhibitory systems, with abnormalities in glutamatergic pathways, has been implicated in the pathophysiology of autism. In addition, chronic redox imbalance has been linked to autism. NAC is a glutamatergic modulator and also functions as an antioxidant. In the present study, supplementation with NAC as an adjunct to risperidone improved irritability and hyperactivity/noncompliance in children with autistic disorders.

Nikoo M et al. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Clin Neuropharmacol.* 2015;38:11–17.

Selenium for Age-Related Cognitive Decline

Thirty-one elderly Brazilian individuals (mean age, 78 years) who had mild cognitive impairment were randomly assigned to consume 1 Brazil nut per day (providing daily an estimated 289 μg of selenium) or no Brazil nuts for 6 months. At baseline, the serum selenium concentration was below normal in all but 1 participant. Twenty individuals completed the trial. Serum selenium levels increased in the Brazil nut group but not in the control group. After 6 months, improvements in verbal fluency ($p = 0.007$) and constructional praxis ($p = 0.03$) were significantly greater in the Brazil nut group than in the control group.

Comment: Brazil nuts are among the richest dietary sources of selenium. In the present study of elderly individuals with low serum selenium levels and mild cognitive impairment, consumption of 1 Brazil nut per day for 6 months had a positive effect on certain measures of cognitive function. Although Brazil nuts contain many nutrients other than selenium, the amounts present in 1 nut are presumably not sufficient to produce a measurable effect on cognitive function. Therefore, the improvements observed in this study are probably due to the selenium.

The selenium content of the Brazil nuts used in this study was analyzed by flame atomic absorption spectrometry, but according to other sources, the selenium content of Brazil nuts is much lower (50–80 μg per nut). Because of these discrepancies, it is not clear how many Brazil nuts one should consume if the goal is to improve selenium status without risking selenium toxicity. Therefore, it may be better to use selenium supplements than to consume an unknown amount of selenium from Brazil nuts.

Rita Cardoso B et al. Effects of Brazil nut consumption on selenium status and cognitive performance in older adults with mild cognitive impairment: a randomized controlled pilot trial. *Eur J Nutr.* Epub 2015 Jan 8.

Dietary Fatty Acids and Migraines

Sixty-seven adults (mean age, 42 years) with chronic headaches (93% of which were migraines) occurring a mean of 23 days per month were randomly assigned to 1 of 2 intensive dietary interventions for 12 weeks: a diet low in omega-6 fatty acids and high in omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or a diet low in omega-6 fatty acids and containing the low amount of EPA and DHA present in a typical US diet. Both groups achieved targeted intakes of omega-3 and omega-6 fatty acids. Compared with the diet low in omega-3 fatty acids, the diet high in omega-3 fatty acids produced a greater improvement in the mean Headache Impact Test score (-7.5 vs. -2.1; $p < 0.001$), the number of Headache Days per month (-8.8 vs. -4.0; $p = 0.02$), and the number of headache hours per day (-4.6 vs. -1.2; $p = 0.01$).

Comment: Some, but not all, previous studies have found that supplementing with fish oil (which contains high concentrations of EPA and DHA) can reduce the severity and possibly the frequency of migraines. The results of the present study suggest that these benefits can also be achieved by increasing dietary intake of EPA and DHA. The dietary modifications employed in this study included a reduction in intake of omega-6 fatty acids. That component of the diet may have been important, because high intake of omega-6 fatty acids can interfere with the effects of omega-3 fatty acids.

Ramsden CE et al. Targeted alteration of dietary n-3 and n-6 fatty acids for the treatment of chronic headaches: a randomized trial. *Pain.* 2013;154:2441–2451.

High-Dose Biotin for Multiple Sclerosis

Twenty-three French patients with primary or secondary progressive multiple sclerosis received 100 to 300 mg per day of biotin for 2 to 36 months (mean, 9 months). Ninety percent of the patients had various clinical improvements, including improvements in visual acuity, homonymous hemianopia, and spinal–cord related manifestations. In all cases, improvement was first observed after 2 to 8 months of treatment.

Comment: Biotin is a cofactor for acetyl-CoA carboxylase, a potentially rate-limiting enzyme in myelin synthesis. In the present study, most of the patients showed clinical improvement with high-dose biotin. However, since there was no control group, it is possible that the improvements were due to a placebo effect or to spontaneous fluctuations in disease activity. Nevertheless, biotin appears to be safe even in high doses, so a clinical trial may be appropriate for selected patients with multiple sclerosis. According to the authors of this study, 2 double-blind trials of biotin are in progress.

Sedel F et al. High doses of biotin in chronic progressive multiple sclerosis: A pilot study. *Mult Scler Relat Disord.* 2015;4:159–169.

◆

War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

About 1 year ago, I was diagnosed with type 2 diabetes (T2D). At the time, I had all the classic symptoms, such as an unquenchable thirst. My blood glucose was 390! My hemoglobin A1C (a measure of the average blood glucose over the previous 3 months) was 12.3 (which works out to an average of 306). My fasting glucose was 164 (anything over 99 is considered abnormal).

For the past year, I have taken a reading of my blood glucose upon arising as well as several times during the day. Now, my fasting glucose score averages 82. (This morning it was 78.) By point of reference, the medical authority Richard K. Bernstein, MD, believes that 83 is the optimal normal blood sugar score for a healthy adult male. In parallel, my weight has gone from 203, before the diagnosis, to 162 – a more than 40-pound loss. My "orthodox" primary care physician recently scratched his head and declared me "cured" of diabetes. I corrected him with the proviso that if I returned to my previous lifestyle, my diabetes would almost certainly return.

I want the reader to understand that I accomplished this without the use of *any* pharmaceuticals for diabetes (such as insulin or metformin) and just a few basic food supplements.

So how did I accomplish this? The brief answer is that I went on a low-carbohydrate, high-fat diet. This approach flies in the face of the idea that carbohydrates are somehow "essential" nutrients. I choose my foods based on their effect on my blood sugar – in effect, I "eat to the meter." I therefore completely eliminated sugar and other sweeteners, cut out all grains (even including, for now, whole grains), and severely limited my intake of fruit and root vegetables. I do eat other green vegetables and salad greens, with olive oil and plain vinegar dressing. All my blood and urine markers have improved and my cholesterol, although somewhat higher, is of the protective "fluffy particle" kind (pattern A), according to the "VAP" test. I feel great and yesterday went for a 3-hour bicycle ride. Maybe it will work for you.

The photo on the left is from a trip to Europe not long ago. The second was taken in the summer of 2015. Judge for yourself.

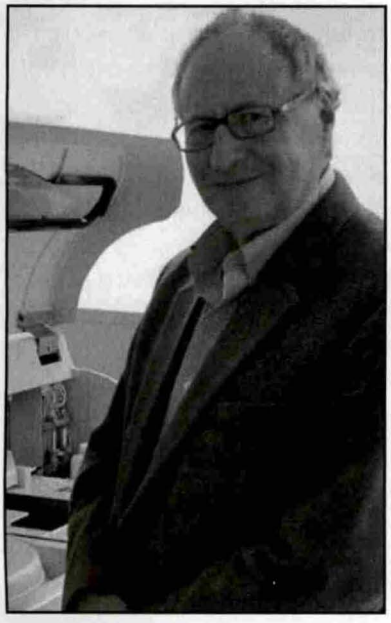

Figure 1: RWM a few years ago.

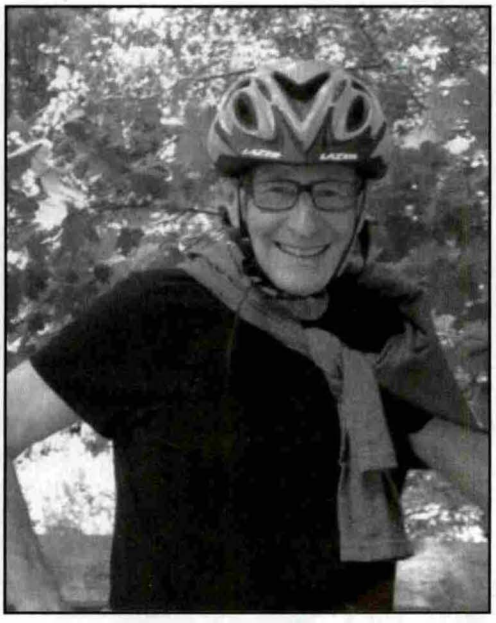

Figure 2: RWM today.

There are many ways to learn about this sort of program. For example, check out the website www.dietdoctor.com for many educational videos on this way of eating and living.

Consultations

As in the past, I am generally available for half-hour or 1-hour phone consultations on cancer treatment options. I am not a medical doctor but know about many of the resources that are available to cancer patients, either locally or in far-flung locations.

To set up an appointment, please e-mail anne@cancerdecisions.com, or call 800-980-1234 or 814-238-3367

➤

War on Cancer

➤

Herbes de Provence Against Aging

> God Almighty first planted a garden. And indeed it is the purest of human pleasures. It is the greatest refreshment to the spirits of man; without which, buildings and palaces are but gross handiworks. ...
>
> – Sir Francis Bacon (1561–1626)

In summer, my thoughts naturally turn to the garden. I have partial responsibility for a community vegetable garden as well as various plantings around two family houses. But, for myself, I maintain a collection of about a dozen culinary herbs. Lately, I have become intrigued by the medicinal properties of some of these aromatic plants. I have always been vaguely aware of their health-promoting aspects, but this line of thinking was stimulating by reading some of the papers of D. James Morré, PhD. Jim and his wife, Dorothy Morré, are professors emeriti of Purdue University in West Lafayette, Indiana. I recently wrote about their fascinating work on ENOX2 and the ONCOblot test. But, in parallel with this, the Morrés have been working on the topic of aging. They found that certain culinary herbs – specifically summer savory – have an extraordinary power, in the laboratory, of countering proteins associated with the aging process. In a YouTube talk, Jim Morré suggested that these herbs might even be responsible for the so-called French paradox. This is the fact that French people often eat a diet that is relatively rich in saturated fats but have a relatively low incidence of coronary heart disease (CHD).

What herbs do I grow? As I said, summer savory, but also winter savory; apple and pineapple mint; spearmint; marjoram; fennel; and of course the ever-popular quartet of parsley, sage, rosemary, and thyme. I was happily surprised to learn, on a recent visit to George Washington's Mount Vernon, that 200 years before Simon and Garfunkel wrote their song, these were the four main herbs in our first president's capacious kitchen garden.

Jim and Dorothy Morré came to this topic through a decade-long search for the molecular source of the biological clock. In 2002, they published their conclusions in the journal *Biochemistry*: "There is compelling evidence," they wrote, that "ECTO-NOX proteins are the ... drivers of the cellular biological clock." The phrase *ECTO-NOX* was later simplified to *ENOX*. This became the basis of their ONCOblot test for cancer. They also discovered an aging-related cell-surface protein (aging-related NADH oxidase or, more briefly, arNOX). ArNOX generates harmful free radicals and is shed from the cell surface. It is found in saliva, urine, perspiration, and interstitial fluids. ArNOX activity, they reported, "correlates with age and reaches a maximum at about age 65 in males and 55 in females." They then set about cloning arNOX proteins and also developing some anti-aging formulas based on arNOX inhibition (Morré 2010).

Astonishingly, some of the things that we normally have in our gardens or kitchen cabinets proved to be particularly proficient at inhibiting arNOX. This is a main subject of many of the Morrés' scientific papers, their book on the subject, and a US Patent Application (US20120207862 A1) titled "Oral Inhibitors of Age-Related NADH Oxidase (arNOX), Compositions and Natural Sources." The Morrés have patented a supplement formula for both skin and internal use.

The Morrés' patented formula contains one or more of the following: basil (*Ocimum basilicum*), lavender (*Lavandula angustifolia*), marjoram (*Origanum majorana*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*) and/or fennel seed (*Foeniculum vulgare*), and/or tarragon, especially French tarragon (*Artemisia dracunculus*).

My local plant nursery has all of these for sale for about $2 apiece. You can also buy seeds from any reputable dealer. Some of these are common indeed, but the originality of the patent lies in its scientific rationale for their use as well as the unique proprietary combination of herbs in the formula. But we can get some hint of the relative merit of these herbs from the Morrés' scientific publications, especially their textbook on the topic (2013).

For testing purposes, these herbs were prepared as hot water infusions of 125 mg per mL of boiling hot water. In other words, herbal tea!

The degree of inhibition of arNOX activity was as follows:

Savory: 89%	Basil: 82%
Tarragon: 82%	Marjoram leaves: 50%
Rosemary leaves: 59%	Sage: 54%

The inhibition of harmful lipid peroxidation ranged from 70% for sage to an incredible 100% for savory (100% inhibition not being a number seen very often in a scientific paper!) Equally amazing, savory and tarragon "were effective at concentrations as low as 75 ng/mL in the assay" (Morré 2013). Needless to say, 75 nanograms is a very, very small amount. What this proves is that (as generations of French cooks would affirm) even a pinch or two of these powerful herbs can have anti-aging effects, especially if taken over a period of time.

I have grown dozens of summer savory plants on my patio. What I do not use fresh I dry or freeze for use throughout the winter. This becomes part of my *herbes de provence*, a mixture of dried herbs typical of the Provence region of southeast France, which I work into as many dishes as I can. I may not live forever, but it won't be for lack of trying!

Itraconazole vs. Cancer

There is a great deal of promise of Food and Drug Administration (FDA)-approved medications repurposed for use against cancer. For example, there is increasing interest in using the approved antifungal medicine itraconazole (Sporanox) as a treatment for cancer. Let's review the scientific basis for this idea.

If you search in the US government's PubMed index of medical literature, you come across about 750 articles that reference itraconazole and cancer. Limiting this to clinical trials brings the total down to about 80. Of course, many of these articles refer to preventing fungal infections in cancer patients, not to the use of the drug as a cancer treatment per se. But over the years, it has been found that itraconazole also has other effects, such as having antiangiogenic activity (i.e., preventing new blood vessel growth).

According to a recent report from the Anticancer Fund in Belgium (affiliated with Reliable Cancer Therapies), "Clinical trials have shown that patients with prostate, lung, and basal cell carcinoma have benefited from treatment with itraconazole, and there are additional reports of activity in leukemia, ovarian, breast, and pancreatic cancers" (Pantziarka 2015).

At Stanford University, Daniel J. Kim and colleagues have been exploring the use of oral itraconazole as a treatment for basal cell carcinoma. The rationale behind this is that the oddly-named Hedgehog (HH) signaling pathway, which is a "crucial driver of basal cell carcinoma (BCC) tumorigenesis," is inhibited by itraconazole. The drug has also been found to reduce BCC growth in mice.

In this phase II clinical trial, 29 patients were enrolled, of whom 19 were treated with itraconazole. The treatment was associated with two incidents of adverse effects – one case of moderate fatigue and one more serious grade 4 incident of congestive heart failure.

But overall in the 19 treated patients, itraconazole reduced cell proliferation by 45%, HH pathway activity by 65%, and the tumor area by 24%. Of 8 patients who had multiple tumors, 4 achieved partial responses, and 4 had stable disease. Tumors from untreated control patients, and from those previously treated with another drug (vismodegib), showed no significant changes in proliferation or tumor size.

The Stanford authors concluded that "itraconazole has anti-BCC activity in humans, especially in those tumors marked by the HH signaling pathway" (Kim 2014).

In 2011, Blake T. Aftab, PhD, of Johns Hopkins University, similarly wrote: "[D]ata suggest that itraconazole has potent and selective inhibitory activity against multiple key aspects of tumor-associated angiogenesis in vitro and in vivo, and strongly support clinical translation of its use. Based on these observations, we have initiated a randomized phase II study comparing the efficacy of standard cytotoxic therapy with or without daily oral itraconazole in patients with recurrent metastatic NSCLC [non-small cell lung cancer]."

A total of 23 patients were enrolled in this study. At 3 months, 67% of the lung cancer patients on itraconazole plus the drug pemetrexed (Alimta) were progression free vs. 29% on the control arm of pemetrexed alone. Median progression-free survivals were 5.5 months (itraconazole) versus 2.8 months. Overall survival was longer in patients receiving itraconazole (median 32 months) versus control (8 months). You read that right – a 4-fold increase in median overall survival, with no differences in toxicity between the two study arms! This is definitely a drug to watch.

Itraconazole costs about $8 per 100 mg capsule over the Internet. While hardly free, it is far less costly than many "targeted" anticancer agents, which now are priced through the roof. For example, according to a statement by 100 leading hematologists/oncologists (quoted at the Harvard Law website): "Of the 12 anti-cancer drugs approved by the FDA last year, 11 were priced above $100,000. This represents a doubling of prices from a decade ago. The authors claim that these prices 'are too high, unsustainable, may compromise access of needy patients to highly effective therapy, and are harmful to the sustainability of our national healthcare systems'" (2013).

Amen! But one has to wonder whether a relatively cheap drug such as itraconazole has any chance at all of development in the monopolistic cancer drug marketplace.

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For a Purdue press release on the Morrés from a dozen years ago: Purdue researchers discover basis for biological clock. http://www.purdue.edu/uns/html4ever/030106.Morre.bioclock.html.

Resources

For the Morrés' cancer test and treatment:
ONCOblot test: http://oncoblotlabs.com.
Capsol-T treatment: http://www.capsol-t.com.

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

How Much Salt?

by Jacob Schor, ND, FABNO

In the practice of medicine, we advocate for rational, objective, unbiased decision-making that favors the best interests of our patients. At least this is what we claim. Yet the reality is often different, and we often fragment into different camps adhering to one side or another of debates regarding specific practices. Far from being dispassionate and objective arbiters of the science, we often take sides and defend our beliefs in a manner that is far from dispassionate; our behaviors appear more comparable to those defending their religious beliefs rather than those engaged in the rational advancement of knowledge.

These rather serious thoughts are prompted by the ongoing debate over the simple question of how much salt people should eat. Or more accurately stated, how much salt we as physicians should tell people to eat – or to not eat. Most people eat plenty of salt, and our job is supposed to be to tell them to eat less of it.

This "salt debate" and the intensity of the positions taken is worth watching, not just because it would be useful for us to know what to tell our patients but also to observe the process unfold, to see the battle lines drawn, and to witness how quickly supposedly rational people lose hold of objectivity. Knowledge keeps changing, and to practice good medicine, our understanding of what is "right" must change and evolve with the science. This does not come easily for many of us. Thus, watching this evolution of thinking regarding salt may help us learn to adapt to new understandings in other areas of medicine as well.

The idea that the public should limit sodium intake through reductions in dietary salt intake was introduced in 1972 when the National Institutes of Health started the National High Blood Pressure Education Program. At the time, available evidence to support such a recommendation was weak: a rat study. The problem is that nearly half a century later, the evidence is still weak; it seems that the suggestion to limit salt has been so often repeated that most people, patients and doctors alike, assume that the idea is well proven.

Regardless of the evidence or lack thereof, the NIH and the American Heart Association's position about sodium remains rock solid; reading their position statements, one would assume that the evidence was unquestionable:

"This evidence is extensive – from clinical therapeutics, animal experimentation, physiology and pathophysiology, cross population and within population epidemiologic research, anthropology and randomized controlled trials."[1,2]

Yet, according to Gary Taubes, writing in the *New York Times*, "The USDA, the Institute of Medicine, the CDC and the NIH – all essentially rely on the results from a 30-day trial of salt, the 2001 DASH-Sodium study. It suggested that eating significantly less salt would modestly lower blood pressure; it said nothing about whether this would reduce hypertension, prevent heart disease or lengthen life."[3,4]

Actually, since Taubes wrote this, the Institute of Medicine has backtracked from its sodium position releasing a position paper in May 2013 suggesting that current evidence "is not consistent with efforts that encourage lowering of dietary sodium in the general population to 1,500 mg/day."[5]

Our need for salt is a fundamental evolutionary inheritance, a reminder that our ancestors were once ocean dwellers. Our cells still require salt concentrations reminiscent of our past. We still need to bathe our cells in "sea water" to survive. At the same time, the idea that excess salt could be harmful is not unreasonable. High salt consumption causes the body to retain water in order to maintain a constant sodium concentration in the blood. Salty foods make us thirsty, we drink more water, and for a short period, blood pressure increases until the kidneys can excrete the excess salt and water. As high blood pressure is a risk factor for cardiovascular disease (CVD), the idea is reasonable that chronic elevated blood pressure caused by high salt consumption over time would increase CVD. The problem again is that there has been little evidence to support this idea.

Jordi Salas-Salvadó, the principal author of a recent study, pointed out that while the "2010 US Dietary Guidelines for Americans recommended a sodium intake below 2300 mg per day [~1 teaspoon of salt] in the general population. ... it is unknown whether decreasing sodium intake below 2300 mg/d has an effect on CVD or all-cause mortality. The recent Institute of Medicine (IOM) [report] explicitly concluded that studies on health outcomes are inconsistent in quality and insufficient in quantity to determine that sodium intake below 2300 mg/d may increase or decrease the risk of heart disease, stroke or all cause of mortality."[6]

In 2014, a Cochrane Review also failed to confirm the current government recommendations. Eight

studies were included in the review: three of the studies were on people with normal blood pressure (n = 3518), while the other five studies had mixed populations of normal and hypertensive participants (n = 3766). There was no significant change in risk of mortality for people with normal blood pressure associated with low salt intake [RR 0.67, 95% confidence interval (CI) 0.40–1.12]. There was a nonsignificant trend toward lower cardiovascular disease related mortality in participants with high blood pressure who lowered salt intake [RR 0.67, 95% CI 0.45–1.01].[7]

A September 2014 meta-analysis by Niels Graudal of Denmark also brought the issue into doubt. Graudal looked at all-cause mortality and CVD in populations exposed to varying amounts of sodium. Data from 23 cohort studies and 2 follow-up RCTs (n = 274,683) showed that risk of mortality or CVD events was about 10% lower in people consuming what the researchers considered a normal amount of sodium (115–165 mmol/day [6728–9653 mg salt or 2¾ tsp to 4 tsp/day)] compared with low sodium intake (<115 mmol < 6728 mg salt or <2 3/4 tsp). Risk of mortality increased about 16% and for CVD events by about 12% in people consuming large amounts of sodium (>215 mmol 12,578 mg salt or 5¼ tsp salt/day).[8] In other words, following the NIH's current suggestion of consuming less than a teaspoon of salt per day was associated with increased mortality and CVD events compared with rather liberal salt use. Thus, in Graudal's view, "For most people, there is no reason to change their dietary habits concerning salt, as most people eat what appears to be the safest amount."[9]

Just as a reminder, the 2010 Dietary Guidelines for Americans recommend a sodium intake below 2300 mg per day (equivalent to just less than 1 teaspoon of salt per day) for the general population. These guidelines rank salt as one of the most dangerous aspects of the American diet, at the top of their list of harmful foods, listing salt even before "solid fats, added sugars and refined grains."[10]

Yet is it as dangerous as the USDA would have us believe? Most importantly, does complying with its guideline to eat less than 2300 mg per day have long-term benefits?

Suggestions that these guidelines might be too conservative over the years have met with strong backlash. Back in 2006, the *Journal of the American College of Nutrition* published a supplemental issue focusing on issues related to salt and raising the issue that the guidelines might be too low.

The Center for Science in the Public Interest (CSPI) attacked the journal almost immediately, accusing it of ethical violations, misrepresenting the science, allowing Frito-Lay and other junk food manufacturers to influence its science.[11] This was an important enough accusation that *Science News* had Janet Raloff, one of its senior editors, investigate the controversy and report on it in detail. In the end, it seems as if CSPI's accusations were for the most part unfounded; rocking the boat and questioning the status quo isn't tolerated.[12]

In a March 2015 paper, Salas-Salvadó attempted to answer the salt question. He and colleagues who have been part of the PREDIMED group used their earlier data to compare sodium intake from food frequency questionnaires to look for an association between incidence of CVD events and mortality with lower sodium consumption. Recall that the 3982 participants in the PREDIMED cohort were all at high risk for cardiovascular disease.

Participants were categorized by sodium intake as low (<1500 mg/d), intermediate (≥1500 to ≤2300 mg/d), high (>2300 to ≤3400 mg/d), or very high (>3400 mg/d).

Deaths and CVD events were measured for a median of 4.8 years. Sodium intake <2300 mg/d was associated with a 48% lower risk of all-cause mortality after 1 year and 49% decrease risk after 3 years. Increasing sodium intake after 1 year was associated with a 72% higher risk of CVD events.

On the face of this evidence, this study is strong support for the low-sodium guidelines.[13] Yet recall that

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this study involved the PREDIMED Trial Cohort, all of whom were at high risk for heart disease; just over 70% of them were already medicated for hypertension.[14] While only about 51% of hypertensive people are salt sensitive, for them, reducing dietary salt intake will help reduce blood pressure.[15] Reducing salt intake in someone with normal blood pressure does not lower blood pressure and so may not offer the same health benefit. Given that more than half of the PREDIMED cohort had high blood pressure, it is possible that low-salt diets offered the group a benefit not seen for the general population. The findings of this study may not really conflict with the results reported in the Graudal and Cochrane Reviews.

Robert Heaney, a well known endocrinologist specializing in nutrition and a professor at Creighton University, best known for his work on osteoporosis and vitamin D, startled many with an article published in the March/April 2015 issue of *Nutrition Today*. His analysis of the available evidence led him to conclude that health risks increase when sodium intake drops below 3 to 4 grams per day or rises above 6 to 7 g/day (2.5 tsp).[16] (His review is worth reading.)

Of course Heaney's opinion is nutritional sacrilege, and Cheryl Anderson and other mainstream low-salt advocates offered a rebuttal in the same issue of *Nutrition Today*, suggesting that the methodology of the studies Heaney quoted is flawed.[17]

What will the final outcome of these salt debates be? It is too early to tell. As a naturopathic physician, I admit my own bias to favor the underdog; my tendency is to be drawn to the "alternative viewpoint," to want the mainstream science to be proved wrong.

Likely, as is often the case, the biology may prove more complex than we at first thought. Salt reduction may prove valuable for some, less so for others, and harmful for others. Learning to determine where and when to apply salt restriction will become another aspect to our art of practicing medicine. In the meantime, the real lesson comes from watching the participants of this ongoing debate: who is practicing good science and good medicine, and who is acting merely to defend a belief system whose foundation is no longer as solid as we assumed?

Conversion of Salt Units

Any discussion about ideal salt intake is confused by the variety of units used to measure consumption. Conversion factors are below. In my commentary above, all amounts have been converted into teaspoons of salt rounded to the nearest ¼ tsp.

- 1 mmol sodium = 23 mg sodium
- 1 g sodium = 43.5 mmol sodium
- 1 g salt (sodium chloride) = 390 mg sodium
- 1 tsp salt = 6 g salt ≈ 2400 mg sodium = 104 mmol sodium = 104 mEq sodium

To convert mmol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weights of sodium, chloride, and sodium chloride), respectively.[18]

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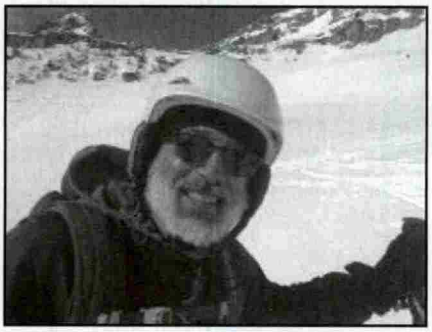

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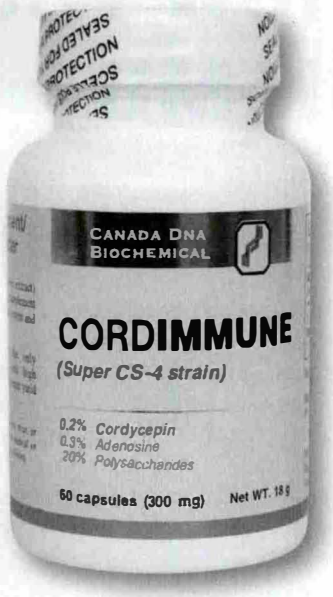

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Sepsis in the Hospital and High-Dose Intravenous Ascorbic Acid: Interview with Alpha A. Fowler III, MD

by Kirk Hamilton

Kirk Hamilton: Can you please share with us your educational background and current position?

Alpha A. Fowler, III, MD:

- Medical School: Medical College of Georgia, Augusta, Georgia (1971–1975)
- Internal Medicine Residency: Virginia Commonwealth University, Richmond, Virginia (1975–1979)
- Fellowship in Pulmonary Disease and Critical Care Medicine: University of Colorado Health Science Center, Denver, Colorado (1979–1982)
- Current Position: Professor of Medicine, Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University School of Medicine; Director, VCU Johnson Center for Critical Care and Pulmonary Research (1982–present)

KH: What got you interested in studying the role of intravenous ascorbic acid (AA) in sepsis patients?

Alpha A. Fowler: I and my colleagues have had a 30-year research interest in sepsis and the acute lung injury which occurs following the onset of sepsis. Approximately 5 years ago, we discovered using experimental animals with sepsis and lung injury that ascorbic acid would dramatically attenuate the extent of the inflammatory response in these animals and would significantly improve survival of the animals. Due to the inability to achieve significant blood levels of AA when AA is administered by the oral route, we administered AA to the animals "parenterally" (non-orally) by injecting the AA into the peritoneum of the animals. AA was rapidly absorbed into the circulation achieving high blood levels. The very significant experimental work we performed in the laboratory all pointed to AA's effects being very powerful and potently anti-inflammatory. We summarized AA's effects in several research publications. We then proposed to VCU's Institutional Review Board to perform a trial in critically ill patients who had developed bacterial sepsis. As you know from reviewing our *Journal of Translational Research* publication, the trial was highly successful.[1]

KH: What is the morbidity and mortality of septic patients in hospitals generally?

AAF: Patients with severe sepsis suffer higher mortality rates compared to patients with organ failure but no sepsis. Despite over 15,000 patients studied and over $1 billion in study costs, effective sepsis therapy remains elusive. The average mortality rate from bacterial sepsis is approximately 45%. Patients who survive sepsis have a very high morbidity rate with persisting organ failure (i.e., renal failure, myocardial infarction, stroke, liver injury, persisting lung fibrosis, and the need for oxygen therapy).

KH: What is the biochemistry of AA that might alter the pathophysiology of sepsis? Anti-inflammatory? Anti-infective? Prooxidant? Antioxidant?

AAF: My research colleagues and I have extensively documented the potent effects of AA. Importantly, AA "downregulates" or attenuates the extent of the inflammatory response that occurs in sepsis. Critical pro-inflammatory proteins that are released into the bloodstream following the onset of sepsis are very significantly attenuated. AA does this by blocking the activation of an important transcription factor (nuclear factor-kappa B) that drives the "expression" of the genes which lead to surges of the various inflammatory proteins in the bloodstream after sepsis starts. We have demonstrated in experimental animals that AA is anti-infective. We determined this by sampling the blood of septic animals who received AA. Blood was cultured from animals who did not receive AA or animals who received AA. The treated animals had a much lower incidence of positive blood cultures. AA is well known to be a potent antioxidant.

KH: Where did you come up with a daily dose of 50 mg/kg/24 h and 200 mg/kg/24 h? For a 70 kilogram person, that is 3500 mg and 14,000 mg of AA intravenously over a 24-hour period respectively. Is that correct? And then, if I understand correctly, that dose was split into 4 doses (1 every 6 hours) and each one of those doses of AA was put in a 50 ml bag of D5W kept in the refrigerator and administered

with light protected tubing? Am I getting this therapy picture correctly?

AAF: Yes, that's correct. I would also add that the 50 ml bag containing the drug was kept hooded from the time the drug left the refrigerator until all the drug was infused; the hood stayed on to prevent any oxidation of the AA. We determined/approximated the daily effective dosage from our animal studies. When we took AA into our clinical trials, we really did not know what exact dosage would be effective. We selected the two dosages by what we expected the resulting drug level to be. We didn't really have any guidance, we literally just experimented to arrive at the top dosage level. The total daily dosage of AA was divided into 4 aliquots and administered IV every 6 hours. So each patient who received AA received 4 infusions daily for 4 days.

KH: Were blood levels of AA or other biochemical markers taken before, during, or after the intervention? If so did they correlate with symptoms and supplementation with AA?

AAF: Great question. We took baseline AA blood levels and baseline inflammatory biomarker levels before AA was administered. The study we conducted in human subjects was a double-blind, placebo-controlled trial, so we did not know what the patient was receiving. We repeatedly sampled blood for AA blood levels and inflammatory biomarkers at 12, 24, 36, 48, and 96 hours. When we unblinded the data we had gathered on each patient, we found that there was a very significant correlation with blood AA levels. The patients who received AA exhibited rapid improvement in organ failure that had been caused by sepsis. The high dose of AA produced the most dramatic effects and resulted in the rapid correction of organ failure that was assessed by the Sequential Organ Failure Assessment (SOFA) score. Patient who received placebo (sugar water) had no change in the extent of their organ failure. We also observed that patients who received AA exhibited prompt reduction in the inflammatory biomarker levels.

KH: Can you tell us about your study and the basic results?

AAF: The study examined patients with severe sepsis in the Medical Respiratory Intensive Care Unit at Virginia Commonwealth University Medical Center. The patients we studied were all critically ill with severe sepsis. We studied 24 patients with 8 patients being randomized to placebo, 8 patients randomized to low dose AA (50 mg/kg/day for 4 days), and 8 patients randomized to high-dose AA (200 mg/kg/day for 4 days). The study was a double-blinded, placebo-controlled trial. The "blind" was maintained by VCU Health System's Investigational Pharmacy. The trial was a huge success due in large part to VCU's Critical Care Nursing. They assured that "study drug" would be administered every 6 hours for the 4-day treatment protocol.

KH: Did the low dose of AA at 50 mg/kg/day arm of the study have as much positive anti-inflammatory effects from biochemical marker change and reduce SOFA scores as the higher dose of 200 mg/kg/day did? In other words, if the 200 mg/kg/day arm resulted in better clinical and biochemical results in these septic patients, would more vitamin C in mg/kg/day work better, or at least be warranted as a therapeutic trial to see if there is a greater clinical effect? Because I can assure you that a higher dose of intravenous AA can be given safely from the 1000s of anecdotal clinician infusions over the last 75 years since the time of Dr. Frederick Klenner, who pioneered IV vitamin C.

AAF: As you know, we tested two different dosages of AA. With the 200 mg/kg/day, we saw a very significant impact on the SOFA score. The 50 mg/kg/day AA dosage had an impact on the SOFA score as well. SOFA scores on the lower-dosage AA dropped but not to the same statistical extent. The high-dosage AA reduced SOFA scores significantly at days 1 through 4. Low-dose AA infusions also reduced the SOFA score each day but not to the same extent. We tested three biomarkers. C-reactive protein and procalcitonin are markers of inflammation. Both the high- and low-dosage AA significantly reduced these biomarkers. Low- and high-dose AA significantly reduced C-reactive protein to the same extent. It was the high-dose AA that had the most profound effect on the inflammatory biomarker procalcitonin, reducing the blood level significantly by day 2. But very importantly, we quantified a protein called *thrombomodulin*. Thrombomodulin is a protein normally bound to the surface of endothelial cells and not found free in the circulation. If the blood level of thrombomodulin rises, this is a surrogate marker of vascular injury. In this study, we found that thrombomodulin blood levels in patients randomized to placebo began to rise 24 hours after entering the study. The rising blood levels of thrombomodulin indicated severe vascular injury in the placebo patients. The thrombomodulin levels in both low- and high-dose AA-treated patients never rose. This indicated that both low- and high-dose AA protected the vasculature in patients with severe sepsis.

The question, would more vitamin C in mg/kg/day work better, or at least be warranted as a therapeutic trial to see if there is a greater clinical effect? may be answered in time. However, performing clinical trials in critically ill human subjects is an arduous task. The regulatory steps that one has to proceed through in our current environment when studying humans seem to be never ending. This is understandable, due in very large part to concerns for patient safety. We are excited by our results and are very pleased that we were able to reduce the SOFA score and biomarker levels with 200 mg/kg/day AA infusions. Although our study was not powered to examine mortality, we did see mortality fall from 62.5% in placebo patients to 38% in vitamin C-treated patients. Some researchers have noted that extremely high doses of AA are prooxidative rather than being antioxidative. We are for the present going to stick with the high-dose AA we reported.

KH: Were there any side effects with the AA therapy? How was the patient compliance?

AAF: No adverse events occurred in critically ill patients who received AA. Patients who were critically ill were studied. Compliance was not an issue. Study drug was administered on time by Critical Care Nursing.

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KH: Who is a candidate for AA therapy? All subjects with heart failure? All subjects with diseases of the heart where there is a reduced ejection fraction?

AAF: AA can be administered to all patients with sepsis. Heart failure was present in several patients who received AA. No adverse event occurred.

KH: I am thrilled about your work and have been waiting a long time to see larger doses of ascorbate used intravenously for acute illness, but you are probably well aware while these are very large doses for conventional medical care, these are small doses of intravenous vitamin C for those practitioners who used it regularly. AA at 30 to 100 grams IV are "not uncommon" intravenous doses in integrative medicine practices? Can you comment, please?

AAF: We are well aware of the literature and the dosages of AA that have been reported by physicians engaged in various studies (i.e., cancer). The AA dosage protocol we administered to septic patients emerged out of carefully performed scientific investigation. You can refer to the scientific papers we have published using the dosage we arrived at.[2–7]

KH: What was the solution with vitamin C? D5W, sterile water? Were there any added nutrients as well to the ascorbate solution?

AAF: AA (vitamin C) was prepared by VCU Medical Center's Investigational Pharmacy in 50 ml aliquots. AA was mixed with dextrose 5% and water. Once the AA solution was prepared, the aliquots to be administered were kept at 4 °C in the dark. The 50 ml aliquots had a light protected hood placed over the bag. When AA was to be infused, the hooded AA aliquot was taken from the ICU refrigerator and infused into the patient in light-protected tubing over 30 minutes. All these measures were taken to prevent AA from spontaneously oxidizing, which it will do if these measures are not addressed. No nutrients were added to the AA solution.

KH: How can the public or health professionals use this information?

AAF: We feel that AA infusion into critically ill patients is a totally overlooked form of therapy. AA to treat bacterial and fungal sepsis is a form of therapy which has been "hiding in plain sight." We are hopeful that AA infusion to treat severe sepsis will emerge into the standard of care for this patient population. We are currently conducting an NIH-sponsored double-blind, placebo-controlled trial examining specifically the effectiveness of AA to treat sepsis-induced acute respiratory distress syndrome (ARDS). This trial is a phase II trial in which Virginia Commonwealth University School of Medicine Pulmonary Disease and Critical Care Medicine Division is the lead center. Participating centers are Critical Care Medicine at Emory University, Critical Care Medicine at the Cleveland Clinic, and Critical Care Medicine at the Medical College of Wisconsin. The results of this trial will be published within the next two years.

KH: Do you have any further comments on this very interesting subject?

AAF: We currently are expanding our research with AA infusions further into human subjects. We have phase I trials using AA in patients post open heart surgery, patients with post closed head injury, and patients post cardiac arrest. We are at work designing a trial to examine AA infusion in patients post bone marrow transplant. All these various patient populations have a high incidence of organ injury.

KH: Can't wait to see the research. Send the published results on any AA IV infusion in hospital care as soon as published and I would love to interview you or your colleagues on that topic. You are doing a great service putting this safe, cheap, and simple therapy to scientific rigor, which, in my opinion, would/will save thousands of lives and millions, if not billions, of dollars in health-care costs.

AAF: You are right about that. The US Food and Drug Administration 2½ years ago removed a product called activated protein C from the market. Activated protein C was used to treat patients with severe sepsis, the identical patients we used AA to treat. Virginia Commonwealth University Health System's charge for a 96-hour infusion of activated protein C was greater than $30,000. Activated protein C, besides being expensive, was associated with a high incidence of adverse events. We calculated the cost of AA we used in the Phase I Sepsis Trial. We could treat the identical patients for less than $1000. So you are right. AA as a therapy for sepsis is safe and inexpensive compared with other drug costs in the ICU environment.

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Nrf2 Is a Master Regulator of Cytoprotective Responses Including Antioxidant, Anti-Inflammatory, Detoxification, Improved Mitochondrial Function, and Autophagy

by Martin L. Pall, PhD, and Stephen Levine, PhD

Nrf2 (nuclear factor erythroid-2; a name derived from its role in erythropoiesis) has been known for some 15 years to be an important transcriptional activator of antioxidant genes, producing therefore important antioxidant protective responses. It has also been known for about 15 years to be activated by many (but not all) phenolic antioxidants, so that much of the antioxidant effects of these compounds are produced through this regulatory response, rather than exclusively through direct antioxidant chemistry. However, it has been shown in recent years that the cytoprotective effects of Nrf2 go far beyond antioxidant effects. They include anti-inflammatory effects, detoxification mechanisms for a wide variety of xenobiotic toxicants, improved mitochondrial function, and autophagy, a process by which both toxic protein aggregates and dysfunctional organelles can be degraded. And it has also been shown in recent years that many health-promoting factors other than phenolic antioxidants act to raise Nrf2 activity. Most of these recent findings have been reviewed in a whole series of recent reviews, and it is the role of this article to summarize the vast scope of these new findings, including the health-promoting and disease-preventing effects of Nrf2.[1-22]

Diseases Prevented and/or Treated by Raising Nrf2, at Least in Animal Models

There are an amazing number of diseases (Table 1) that have been shown to be prevented and/or treated by raising Nrf2. Most of these studies have been done in animal models, although there are also an increasing number of human studies being reported.

The finding that raising Nrf2 is useful in prevention and/or treatment of this list of diseases may seem surprising – almost too good to be true. However, these diseases all have both oxidative stress and inflammatory aspects to them, and many of them are also known to involve mitochondrial dysfunction. Protein aggregates have causal roles of several of them, aggregates that may be removed by Nrf2-dependent autophagy. One of us (MLP) has argued that many of these diseases are caused by the NO/ONOO(–) cycle, ➤

Table 1: Diseases wherein Raising Nrf2 Appears to Be Useful in Prevention and/or Treatment in Animal Models and/or Humans

Citations	Diseases
2,4,9,16,22	Cardiovascular disease including atherosclerosis, ischemic cardiovascular disease, vascular endothelial dysfunction, heart failure
2,4,5,6,12,13,19	Neurodegenerative diseases, including Alzheimer's, Parkinson's, ALS, Huntington's disease
2,6,7,15,19	Chronic kidney diseases
2,8,10,20	Type 2 diabetes; metabolic syndrome; obesity
2,8,19,20	Various types of toxic liver disease
2,6,16,21	Chronic lung disease including emphysema, asthma, pulmonary fibrosis
4,14	Sepsis
2,4,16	Autoimmune diseases
2,3,4,13,19	Cancer (prevention)
4,13	Inflammatory bowel disease
4	HIV/AIDS
11,12	Multiple sclerosis
17,18	Epilepsy

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a vicious-cycle mechanism involving oxidative stress, inflammation, and mitochondrial dysfunction, as well as other factors. It is therefore quite plausible that because of the common factors involved in these diseases, the Nrf2 regulatory response may prevent and/or treat each of them.

Gene Activation via Nrf2

Nrf2 is most known for its role in activation of genes having antioxidant effects, acting by binding in the nucleus, along with some other proteins known as Raf to what are called antioxidant response elements (AREs) in the promoter regions of genes. However, these AREs occur not only in promoter regions of antioxidant genes but also genes involved in other functions. While over 500 genes are activated by Nrf2, there are also genes whose activity is lowered by Nrf2, some of which may be regulated by transcription factors regulated by Nrf2 and others through AREs having repressive effects.[4]

Nrf2-Dependent Antioxidant Effects

Among the *antioxidant genes* activated by Nrf2, one of the most commonly studied is the heme oxygenase 1 (HO-1) gene which converts free heme, which has prooxidant effects, into iron, carbon monoxide (CO), and biliverdin, with the last being converted into the antioxidant bilirubin via an activity also raised by Nrf2, the two biliverdin reductase genes.[1,2] The iron produced by heme oxygenase is sequestered by ferritin, since Nrf2 induction of 4 ferritin genes, preventing iron-produced oxidative stress.[1] This coordinate control of multiple genes producing proteins that are functionally linked in producing an important biological response has been found repeatedly in Nrf2-mediated gene regulation. There are also antioxidant responses produced by CO from its regulatory role that will not be considered here.

A second commonly studied antioxidant gene activated by Nrf2 is the quinone oxidoreductase gene (NQO1), which produces an enzyme that prevents semiquinone redox cycling and consequent oxidative stress.[2] Other antioxidant genes activated by Nrf2 are two superoxide dismutase genes (SOD1 and SOD2), which lower oxidative stress by lowering superoxide and also the functionally linked catalase and two glutathione peroxidase genes, each of which lowers H2O2, produced from superoxide by the SODs. So again we see coordinate regulation of multiple antioxidant genes.

Reduced glutathione (GSH) has often been described as the most important low molecular weight antioxidant produced in the human body. Each of the three genes encoding enzymes required for the de novo synthesis of GSH is activated by Nrf2, as is the gene for glutathione

reductase (the enzyme that converts oxidized glutathione [GSSG] to GSH). Genes encoding 8 enzymes that have roles in the synthesis of NADPH, the reductant needed by glutathione reductase are also activated by Nrf2. Other enzymes that have roles in using GSH for antioxidant purposes, including two glutathione peroxidase genes (discussed in the previous paragraph), and the glutaredoxin 1 gene are Nrf2 activated.

Five genes involved in thioredoxin-related antioxidant responses are activated by Nrf2, including peroxiredoxin-1 and -6 which destroy peroxynitrite, an extremely reactive oxidant responsible for nitrosative stress.[1] In summary, it can be seen from the above that there are 23 genes involved in antioxidant protection, each of which is activated by Nrf2. There are in addition still other genes activated by Nrf2 that help remove toxic products of lipid peroxidation and still others similarly regulated that help remove products of oxidative DNA damage in the process of DNA repair.

Anti-Inflammatory Effects of Nrf2

Nrf2 activation produces a wide variety of anti-inflammatory effects, including lowered NF-κB and lowered activity of a series of inflammatory mediators, including cytokines, chemokines, adhesion molecules, COX-2, MMP-9, and iNOS.[15,16] Many of these changes may be indirect effects produced by raising antioxidant responses, but there are also direct anti-inflammatory effects such as raising the anti-inflammatory cytokine IL-10.[5]

Detoxification Genes Activated by Nrf2

Hayes and Dinkova-Kostova list a total of 25 different genes activated by Nrf2, each of which has a role in detoxification of various toxic xenobiotics.[1] Nrf2 has a wide range of detoxification effects, producing increased resistance to toxic xenobiotics.

Mitochondrial Biogenesis and Autophagy

The diseases listed in Table 1 are also characterized by energy metabolism and mitochondrial dysfunction, such that one of the mechanisms that may be included as cytoprotective may be increased mitochondrial biogenesis. Such increased mitochondrial biogenesis has been shown to be produced by Nrf2 activation, acting in part by activating a related gene, Nrf1.[20] A large number of other genes involved in energy metabolism are also activated by Nrf2.[1]

It is also the case that a number of health-promoting nutrients that stimulate Nrf2 also act to increase the process of autophagy by which damaged organelles and also damaging protein aggregates can be degraded proteolytically, with such autophagy occurring in part via a Nrf2-dependent process. This stimulation of autophagy, useful in removing damaged mitochondria, is also useful in removing protein aggregates that have roles in neurodegenerative and other diseases and has antioxidant roles are well. However, it should be noted that autophagy is inhibited by very high levels of Nrf2. It follows from this that Nrf2-dependent autophagy may be useful as a cytoprotective response in multiple ways, one of which has roles in improving mitochondrial function.

Nrf2 Activity Is Raised by Many Health-Promoting Nutrients and Other Factors

The amazing list of health-promoting factors that have been shown to act, at least in part, by raising Nrf2 are shown in Table 2.

Each of the nine factors listed in Table 2 has an extensive literature on its health-promoting effects. Although all nine have been shown to raise Nrf2 activity, several of these can clearly act in other ways not involving Nrf2 to promote health.

For example, four of the nutritional factors are well established to act independently of Nrf2 as follows:

- Phenolics can act as chain-breaking antioxidants.
- Carotenoids can act as scavengers of singlet oxygen and peroxynitrite.
- Fish oil has anti-inflammatory properties by acting as precursors of eicosanoids.
- Exercise can act in ways independent of Nrf2.

However, each of these 9 factors, when tested in Nrf2−/− mouse knockout mutants, has been shown to have lost most of its health-promoting properties as compared with their activity in Nrf2+/+ mice.[32-39] This shows, therefore, that much of their health promotion requires the presence of a functional Nrf2 gene, at least in the mouse. Other cell culture studies on these nutritional factors have also supported an important role for Nrf2 elevation in response to these factors.

Three of these classes of chemicals act via oxidation products to raise Nrf2 levels. The long-chain omega-3 fatty acids DHA and EPA act via their oxidation product 4-hydroxy hexenal to raise Nrf2.[27,28] The carotenoids act, primarily and possibly entirely, via their oxidation products to raise Nrf2.[25,26] And the phenolic antioxidants are thought to act via

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Table 2: Health-Promoting Factors That Act to Raise Nrf2 Activity

Citations	Health-Promoting Factors
2,3,4,5,8,15	Many but not all phenolic antioxidants
2,3,4,5,7,8,15	Isothiocyanates from broccoli, cabbage, and other cruciferous foods
2,4,5,8,15,19,20	Triterpenoids and other terpenes
2,23,24	Sulfur compounds including allyl sulfides in garlic/onion/allium foods
2,25,26	Carotenoids of which lycopene appears to be the most active
3,27,28	Fish oil (long-chain omega-3 fatty acids)
29,30	g,d-tocopherols and tocotrienols (but a-tocopherol has little activity)
3,31	Modest oxidative stress (hormesis)
4,22	Exercise, works in part via modest oxidative stress

their quinone and semiquinone oxidation products in raising Nrf2.[1-6] This pattern is important because it means that each of these will be most active in raising Nrf2 in tissues that are under oxidative stress and therefore in most need of raising Nrf2 to protect themselves from the consequences of oxidative stress and other related cell damage.

The Two Most Healthful Known Diets, the Traditional Mediterranean Diet and the Traditional Okinawan Diet, Are Both Rich in Nrf2 Activating Nutrients

The traditional Mediterranean diet, thought to be ideally described as the Cretan diet of the 1960s, and the traditional Okinawan diet of the same time period, are thought to be the most healthful diets known, with high overall lifespans, large numbers of centenarians, and low incidences of cancer and cardiovascular disease.[40-46] Diets in both of these locations are thought to have become considerably less healthful in recent decades, but studies of these two traditional diets are still important parts of our understanding of dietary factors that may influence human health. The question being raised here is whether nutrients raising Nrf2 activity in these diets are likely to have an important role in their health-promoting properties.

The dietary factors which raise Nrf2 (Table 2) are all of plant origin except for the long-chain omega-3 fatty acids, which are best obtained from seafood. Consequently, it may be argued that the best diets for raising Nrf2 are those with regular seafood consumption but otherwise containing large amounts of foods derived from plants, particularly plants with low calorie densities which are likely to be consumed in larger quantities and therefore provide in general more phytochemicals. Both the traditional Mediterranean and Okinawan diets clearly fit this description.[40-46] Furthermore, several of the nutrient categories known to raise Nrf2 listed in Table 2 are thought to be high in each of these diets (see Table 3).

It can be seen from Table 3 that both of these health-promoting diets are very rich in nutritional components that raise Nrf2, including five of the six types of Nrf2-activating components listed in Table 3. In addition, the traditional Mediterranean diet is most characterized by high consumption of olives and olive oil, which are known to contain very high levels of phenolics and terpenoids, both of which have been shown to raise Nrf2. The main caloric source in the Okinawan diet is the sweet potato, often including purple sweet potatoes; all sweet potatoes are very high in carotenoids, and purple sweet potatoes are very high in anthocyanin phenolics, which are potent Nrf2 activators.[40] Murakami et al. showed that a large number of specific vegetables in the traditional Okinawan diet are potent agents that lower the production of both superoxide and nitric oxide in leukocytes, suggesting agents that act in part by raising Nrf2. In some cases, they implicated both phenolics and terpenoids in producing these responses, again suggesting a possible Nrf2 effect.[41] While it is unlikely that all of the phytochemicals that may produce health-promoting effects in these two diets are acting mainly or solely via Nrf2, it may be the case that Nrf2 has a major role in the health promotion in each of these two diets.

The Okinawan diet is thought to be very similar to what is often called the Paleolithic diet, the diet that our ancestors ate during much of human evolution.[47] The only substantial difference is that in the Paleolithic diet, most of the omega-3 fatty acids come from wild animals and plants, both of which are quite rich in omega-3 fatty acids, rather than more substantially from fish.[48] Specifically, the Okinawan diet closely resembles the Paleolithic diet in having very high levels of phenolic and carotenoid antioxidants as well as high omega-3 levels, probably also terpenoids and essentially no grain consumption, all of which will act to raise Nrf2. It may be argued that we evolved with much higher levels of Nrf2-raising nutrients

Table 3: Overall Apparent Consumption of Nrf2 Raising Nutritional Components[40-46]

Nutrient Component	Traditional Mediterranean Diet	Traditional Okinawan Diet
Phenolic antioxidants	High consumption from olives and olive oil, herbs, legumes, eggplant, many leafy green vegetables	High consumption from soy, many green vegetables and herbs; also provided by purple sweet potato varieties
Carotenoids	High consumption, especially from tomatoes and leafy green vegetables	Very high consumption, especially from sweet potatoes and many leafy green vegetables
Long-chain omega-3 fatty acids	High consumption from fish; also purslane and walnuts provide fatty acid precursors to the human body	High consumption from fish; also leafy green vegetables provide some fatty acid precursors to the human body
Isothiocyanates	Probably average for European diets	High from cruciferous vegetables and daikon radish, but no higher than other East Asian diets
Terpenoids	High from Mediterranean herbs, olives, peel of fruits, and eggplant	Uncertain
Allium-derived sulfur compounds	High consumption of garlic and onions	Relatively high (onions, other allium), probably similar to Chinese diet

in our diets and that almost all of us are currently in a dietary deficiency state for Nrf2-raising nutrients. This may in turn be responsible for much of the extraordinary predominance of chronic diseases afflicting modern populations, characterized by oxidative stress, inflammation, and mitochondrial dysfunction.

Is Nrf2 a Master Regulator of Longevity and Healthspan?

This is what is suggested by the vast array of chronic age-related diseases, as shown in Table 1, that are prevented and/or treated by raising Nrf2. This is what is suggested by the large number of health-promoting factors that act by raising Nrf2. This is what is suggested by the ability to Nrf2 to raise antioxidant, anti-inflammatory, mitochondrial function, and autophagy activities, given the established role of oxidative stress, inflammation, mitochondrial dysfunction, and accumulation of damaged proteins, protein aggregates, and organelles. Each of these last four mechanisms is implicated in the aging process.

This was suggested by Lewis et al. in their paper "Nrf2, A Guardian of Healthspan and Gatekeeper of Species Longevity."[49] They state, "There is mounting evidence across evolutionarily distant species that Nrf2-ARE-dependent components are associated with both longevity and extension of healthspan." These studies include a number of genetic studies in the mouse and in several other species that raising Nrf2 activity produces prolonged lifespans and healthspans and that lowering Nrf2 produces shorter lifespans and healthspans.

How Is Nrf2 Regulated by the Health-Promoting Factors Listed in Table 2?

Each source has reviewed the mechanisms by which Nrf2 is regulated, together with at least a bit of information on how various factors raise Nrf2.[1-22] Their discussions on mechanisms are generally much more detailed than is the discussion here. Consequently, the reader is suggested to go to them and particularly to Hayes & Dinkova-Kostova, Kumar et al., and Baird & Dinkova-Kostova for more detailed information than is provided here.[1-3]

Nrf2 protein, under what have been called noninduced situations, is mostly contained in an inactive complex with another protein known as Keap1. Keap1 has five reactive cysteine residues, in each of which reaction of inducing chemicals with the cysteine thiol can start a process leading to release of Nrf2 from Keap1. Following release, Nrf2 can move into the nucleus, complex with other proteins called Maf, bind to ARE sequences on DNA, and stimulate transcription of adjacent genes. The agents that react with these thiols are electrophilic and/or oxidative, and the reaction with these thiols is thought to be the most important mechanism of regulation of Nrf2. The five different cysteine thiols differ from one another in what compounds they react with.

However, there are many other mechanisms that come into play, making the Nrf2 control system very complex. There are several protein kinases that have roles in regulating Nrf2, including the ERK/JNK pathway, PI3K/Akt/ GSK-3β pathway, protein kinase C, and protein kinase G. In addition, when Nrf2 is bound to Keap1, it tends to be targeted to proteasomal degradation, so that its levels are kept low. Release from Keap1 increases the stability of Nrf2 roughly 7-fold, leading to substantially increased levels. Furthermore, Nrf2 stimulates the transcription of its own gene and also the MAFG gene, thus further stimulating Nrf2-dependent transcription. But there is also a downregulation mechanism – Nrf2 also stimulates transcription of the Keap1 gene, lowering Nrf2 elevation. Another complication is that agents that stimulate the aryl hydrocarbon receptor (AhR) increase Nrf2 transcription, leading to increases in Nrf2 activity, a subject that has only fairly recently attracted much attention.[50]

How then do the agents listed in Table 2 stimulate Nrf2 activity? Isothiocyanates, H2O2 and other oxidants, phenolic antioxidants, long-chain omega-3 fatty acids, and carotenoids act by reaction with Keap1 reactive thiols with the last three of these acting through their oxidation products. Allium sulfur compounds, isothiocyanates, and carotenoids act via ERK stimulation, with the latter two acting via two distinct mechanisms to raise Nrf2. Some flavonoids and other phenolics, including some inactive in the Keap1 reactions, act as AhR agonists, as do some terpenoids. Some terpenoids act by raising PI3K and some act directly in Keap1.

It follows from all this that phytochemicals and other agents can increase Nrf2 activity by reacting either directly or through their products with different cysteine residues on Keap1, by regulating the activity of numerous different protein kinases or by stimulating the AhR receptors. It follows from this that phytochemicals and other agents that act in different ways to raise Nrf2 may be expected to act synergistically together.

Consequently, phytochemically rich diets such as the traditional Mediterranean or Okinawan diet may be more active in Nrf2 activation because of possible synergism than may be suggested from just looking at the activities of their individual phytochemicals.

Can Too Much Nrf2 for Too Long Be Toxic?

In general, as indicated in Lewis et al., raising Nrf2 produces prolonged lifespans in animal studies.[49] In addition, human diets rich in nutrients that raise Nrf2, including the traditional Mediterranean and Okinawan diets, produce longer lifespans and lowered disease incidences. However, there are situations where *chronic high-*

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level Nrf2 stimulation produces pathophysiological responses in the body. Perhaps the clearest, well-documented example of this is where high-level chronic raising of Nrf2 levels by TCDD (dioxin) leads to chloracne.[51,52] TCDD also has other, Nrf2-independent toxic effects, but these acne-like changes in skin properties are clearly caused by excessive, long-term levels of Nrf2, such that chloracne may serve as a marker for excessive Nrf2 stimulation. Arsenite and other arsenicals can also produce similar skin responses, acting via excessive Nrf2 activity, but again arsenite has other Nrf2-independent toxic effects.[52] Both the TCDD and the arsenite effects act through AhR stimulation to produce elevated Nrf2 activity. These skin effects of excessive Nrf2 appear to be caused in part by the elevated sensitivity of keratinocytes to Nrf2. Chloracne may be useful as a clinical marker of excessive Nrf2 activity in patients using agents known to raise Nrf2.

This keratinocyte role also shows up in perhaps the most dramatic effect of excessive Nrf2. It was shown that Keap1 transgenic mouse knockout mutants developed hyperkeratosis in the esophagus and forestomach during gestation, which led to death from malnutrition after birth. This was shown to be caused by excessive Nrf2 activity.[53]

In conclusion, it may be expected that levels of Nrf2-raising nutrients that occur in the Mediterranean or Okinawan diets will produce predominantly health-promoting effects. Nevertheless, very high chronic, long-term Nrf2 elevation can produce pathophysiological effects like almost any regulatory effect taken to extreme. Therefore, one needs to take care not to raise Nrf2 levels too high for too long. Given the great amount of genetic heterogeneity in the human population, some individuals may also be much more susceptible to such pathophysiological effects.

Summary

The list of diseases in Table 1 wherein raising Nrf2 acts to prevent and/or treat the disease, at least in animal models, is truly stunning. But it should not be surprising, given the known ability of Nrf2 to produce a whole battery of antioxidant effects, lower a whole battery of inflammatory effects, and improve mitochondrial function in a series of different ways. Additional roles in raising whole batteries of detoxification responses and autophagic removal of destructive protein aggregates and dysfunctional organelles may also be useful in disease prevention and treatment. Each of these diseases is well established to have oxidative stress and inflammatory causal mechanisms, and most of them also are known to have mitochondrial dysfunction mechanisms. Several of them are known to have destructive protein aggregates as well. Many of these diseases are thought to be what is called a NO/ONOO(−) cycle etiology, including several cardiovascular and neurodegenerative diseases, asthma, multiple sclerosis, and epilepsy.[54–56] Heart failure is now the best documented NO/ONOO(−) cycle disease.[56] The 23rd and most recent disease proposed to be caused by the local impact of the cycle is glaucoma.[57] Because the cycle involves oxidative stress including peroxynitrite elevation, inflammatory aspects, and mitochondrial dysfunction, it should not be surprising that apparent NO/ONOO(−) cycle diseases may be prevented and/or treated by raised Nrf2.

The list of health-promoting factors that each act at least in part by raising Nrf2 (Table 2) is also truly stunning. And the fact that the two most healthful diets known, the traditional Mediterranean diet and the traditional Okinawan diet, are both rich in nutrients that act to raise Nrf2 emphasizes the fact that the Nrf2 regulatory system is likely to be important in real human populations. The role of Nrf2 in determining animal lifespans and healthspans also supports this view. It is probable that the Paleolithic diet was much higher in Nrf2-raising nutrients than are our modern diets. By allaying deficiencies in such nutrients, we may be able to lower the prevalence of many of our chronic inflammatory diseases.

It is our belief that raising Nrf2 is likely to be *the* most important health-promoting approach into the foreseeable future. That is not to say that it is a magic bullet. More is not always better, and other health-promoting nutrients and other agents acting in other ways are likely to act along with Nrf2. Agents that lower NF-κB via Nrf2-independent ways, nutrients that are health promoting in other ways, such as B vitamins and vitamin C, magnesium, and some trace elements are likely to be useful, as are agents such as high doses of the hydroxocobalamin form of B12, which lowers peroxynitrite by lowering its two precursors. Other agents that act to improve mitochondrial function independent of Nrf2 are likely to be useful as well.

It has become almost a fad to denigrate the importance of oxidative stress to medicine. However, the exquisite coordination of the antioxidant enzymes controlled by Nrf2 clearly shows that the importance of oxidative stress may be even greater than many scientists working in the field have long believed. Such a complex and clearly highly coordinated set of mechanisms could not have evolved and been maintained throughout metazoan evolution if it had not been of great importance to our health. The Nrf2 studies also show three other related lessons:

1. Regulatory control of antioxidant proteins may be considerably more important than are direct chain-breaking antioxidant mechanisms.
2. Antioxidant mechanisms should be viewed as functioning together with other cytoprotective mechanisms, including anti-inflammatory mechanisms, improvement of mitochondrial function, autophagy, and detoxification of environmental toxicants.

3. Our modern diets should be viewed as being deficient in Nrf2-raising nutrients, with such deficiencies producing much of the chronic inflammatory disease that afflicts us over much of the world.

Notes added in proof: Since this article was submitted, a much longer paper on the same topic has been published by the authors, a paper that is available full text from the PubMed database.[58] In addition, several other important features of Nrf2 have become clear to the authors. Two genes that regulate human health, the ApoE gene, which influences the occurrence of chronic inflammatory disease (increased susceptibility when carrying the epsilon 4 allele), and the BRCA1 (breast cancer gene), both regulate Nrf2, with lowered Nrf2 activity being associated with increased disease. Additional health-promoting factors, including vitamin D and alpha-lipoic acid, also raise Nrf2.

Notes

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'Lyme Brain': Causes and Solutions

by Nicola McFadzean Ducharme, ND

Introduction

Having worked with Lyme disease patients for the past 10 years, I am painfully aware of the far-reaching and growing problem that it is. Lyme disease involves a myriad of symptoms and manifestations, but one of the most prevalent ones is what we call "Lyme brain." This term encompasses broad-based cognitive decline – memory loss, memory retrieval issues, difficulty with focus and concentration, word retrieval issues, slower processing speeds, and so on.

Lyme brain is not just about cognitive deficits, either. It often involves psychoemotional elements such as anxiety and depression. The majority of my patients experience anxiety and/or depression (usually both). Some people experience panic attacks, obsessive-compulsive tendencies or suicidal thoughts, nightmares and night terrors, rage, and impulsiveness. These too, are tremendously hard to deal with.

To some extent the anxiety and depression are a natural response to a chronic illness such as Lyme. But I also remind my patients that anxiety and depression are also symptoms of Lyme, just as real as joint pain and headaches.

In an article published in *Lyme Times*, 70% of Lyme disease patients report some degree of cognitive dysfunction.[1] In my opinion that is a conservative estimate – amongst my own patients, I see numbers closer to 90%.

What Causes Lyme Brain?

Lyme brain has a number of causes. Firstly, there is the presence of microbes themselves in the brain. Bacteria in the brain are invasive and can invade neurons (nerve cells that conduct electrical impulses) and glial cells (supporting cells of the nervous system that do not conduct impulses).[2,3] That invasion can lead to death of the nerve cells.

Borrelia may also cause demyelination of the white matter in the brain. The myelin sheath is a protective sheath that surrounds the axon of the nerve cell and potentiates nerve impulses. This can also contribute to the early demise of nerve cells.

The second major mechanism of Lyme brain is the inflammatory response. In fact, this may be the most significant mechanism.

When there is a pathogen such as *Borrelia*, the immune system will become active to try and counter the threat and kill the pathogen. This process, while protective, results in inflammation, with chemical mediators such as cytokines and chemokines. These mediators can create an environment of reduced oxygenation, blood stasis and increased coagulation, and a disruption in the normal working of the cells. It is important to note that the infection does not have to be in the brain itself for this to occur – the cytokines from infection in the body tissues can travel to the brain and cross the blood–brain barrier, affecting the brain and causing brain-related symptoms.

The third mechanism is by production of neurotoxins. *Borrelia* and related infections trigger neurotoxin release, particularly when they are killed off by antimicrobials, and this can worsen Lyme brain symptoms. Other neurotoxins can worsen the situation, such as heavy metals, molds, and toxins from *Candida*.

Borrelia may release its own neurotoxin known as BbTox1.[4] It can also trigger increased levels of ammonia, which can act as a neurotoxin (this can be worsened by candidiasis, as well as a metabolic condition called kryptopyrroluria).[5,6]

Another contributing factor to Lyme brain is neurotransmitter imbalance. This may be more of an effect than a cause; however, it is something that I frequently see in my patients.

Neurotransmitters are brain chemicals that transmit impulses from one nerve cell to another. Some neurotransmitters are stimulatory and "awakening," such as norepinephrine and epinephrine, while some are inhibitory and "calming," such as serotonin and GABA. Others such as acetylcholine relate to motor system function, and play a role in emotion, learning and short-term memory. Neurotransmitters influence cognition, as well as emotional states.

Some Treatment Options for Lyme Brain

Now that we have a brief overview of some of the key causes of Lyme brain – the infections themselves, the inflammatory cascade created, toxins, and neurotransmitter imbalances being the main ones – I am going to outline some of my favorite ways to help Lyme brain. Of course, this is just a sampling, as there are many options; but these are the ones I have seen work the best in my patients.

Bicillin L-A

You might be surprised to see an antibiotic at the top of my list; however, Bicillin is the primary therapy I have used and seen tremendous benefit in the Lyme brain symptoms. (Note: intravenous antibiotics can have the same benefit, but they are outside the scope of my practice in California, so I use the injectable instead).

Bicillin L-A is a long-acting penicillin given by intramuscular injection 2 to 3 times weekly. The key here is that it crosses the blood–brain barrier very effectively, far more than oral antibiotics, so it affects the neurological system more than oral antibiotics do. It attacks the spirochete forms of *Borrelia*, so other medications still need to be given for the cell-wall deficient and cyst forms.

Bicillin itself has been around for a long time and is quite well tolerated. An obvious contraindication to its use is penicillin allergy. It can cause powerful Herxheimer reactions, which is a reflection of how well it works. I see more of that than I do actual side effects. Some people Herx after a few days on Bicillin; some people experience a delayed Herx around day 25.

Bicillin injections are not everyone's favorite activity. Some people find it quite tolerable, no problem at all, while others find it uncomfortable. However, it is the medication that my patients tell me "gives them their brain back," so many are willing to go through it to get the benefit.

Smilax Glabrae

Smilax glabrae is one of my favorite herbs in Lyme treatment, especially for helping with Lyme brain. This is due to its ability to cross the blood–brain barrier. The *glabrae* form of *Smilax* is the form with best blood–brain barrier penetration, so that is the form that must be used.

Smilax glabrae helps to offset Herxheimer reactions in 90% of my patients, helping to neutralize neurotoxins. Very rarely, in highly sensitive patients, I have seen it cause a detox reaction, so dosing very much depends on sensitivity levels.

Along with working directly in the brain, *Smilax* can also neutralize endotoxins in the intestines. Many endotoxins are cleansed from the gut by the lymphatic system and liver. Binding the toxins in the gut before they reach the bloodstream helps to minimize the inflammatory response that they can cause.

Another potential role of *Smilax glabrae* is protecting against the harmful effects of toxic metals. One study evaluated the effects of lead acetate on oxidative stress in the brain, and found that *Smilax glabrae* showed significant efficiency in reducing blood and tissue levels of lead. It also increased protective antioxidants such as superoxide dismutase and the ever-important glutathione.[7] Given that many Lyme patients struggle with heavy metals, and given that toxic metals can contribute to Lyme brain, this added benefit makes *Smilax* a great option.

I find that *Smilax* combined with glutathione is my winning combination for supporting Lyme brain. Together they typically have a huge impact, more than any other herbs or supplements that I have found.

Glutathione

Anyone who knows me knows that I'm huge fan of glutathione. Among many other benefits, I have seen it help with Lyme brain in so many of my patients.

Two of glutathione's primary roles are acting as an oxidant and neuroprotective, and as a facilitator of detoxification. Third and less well known is glutathione's ability to support neurotransmitter levels and hence mood. Glutathione is one of the most important substances that I know of in keeping the brain healthy and functioning well.

Glutathione is one of the brain's most significant protectors, functioning as its master antioxidant. While the brain only accounts for 2% of body weight, it consumes 20% of the body's oxygen. Therefore, the brain produces a high proportion of reactive oxygen species. Glutathione is one of the key defenses to counter these reactive oxygen species, which can otherwise be quite harmful, producing oxidative stress and neuronal cell damage.

Along with being the crucial antioxidant for the brain, glutathione plays a significant role in detoxification, combining with toxic elements and allowing their excretion from the body. There are many toxic insults to the brain – including toxic metals, mycotoxins, and pesticides – and all can, and do, deplete glutathione. Poor diet, stress, trauma, chronic infections, aging, medications, and radiation can further deplete glutathione. Yet glutathione is critical in detoxing these toxic agents and countering these biological stressors.

There are also genetic factors that can lead to reduced production of glutathione. This is certainly one of the reasons why some people have such high toxic load and impaired ability to clear toxins from the body.

I do have some patients who do not tolerate glutathione well. Those with extreme sulfur sensitivity may not do well with it, as it is a sulfur-based compound. Certain methylation defects will also make one less tolerant of glutathione. But in my clinical experience, this is the minority. Many patients have told me that their cognitive function has improved immediately upon starting glutathione.

A less well-recognized benefit of glutathione is in balancing brain chemistry. Glutathione makes receptors in the brain more sensitive to dopamine and serotonin – two crucial neurotransmitters for healthy brain function. Further, antidepressants have been found to deplete glutathione, again setting up yet another double-edged sword – the medications taken to try to help depression may worsen one of the contributing factors to the depression itself.

In our population of Lyme patients, with high levels of inflammation in the brain, often coupled with infection

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in the brain, and a myriad of other exogenous toxins, there are frequently depleted glutathione levels. And yet these are exactly the circumstances that create a high requirement for glutathione. I utilize liposomal glutathione in my practice for optimal absorption, along with glutathione given intravenously where possible.

Vitamin B12

When we think of B12, we often think of its energy-boosting properties, and it certainly does have those. But what is less known about B12 is its profound impact on, and benefit for, the brain. This is a double bonus for Lyme patients who have chronic fatigue *and* Lyme brain.

B12 deficiency is widespread but unrecognized. Some people will exhibit neurological limitations at low-normal levels, not just "deficient" levels, so optimizing B12 is key. Testing methylmalonic acid may be a better indicator than serum B12 levels.

One of the important factors is the role of B12 in methylation, a series of biochemical and metabolic pathways that can influence emotional regulation, learning, cognition, and memory. Many Lyme patients are undermethylators and do well with methyl-B12.

Other than its role in methylation, B12 also has several benefits for the brain in and of itself. It has been found to improve blood–brain barrier function in people with cognitive impairment. By measuring proteins in the central nervous system, one study determined that B12 (along with folate and B6) tightened the junctions of the blood–brain barrier. Cognitive function was also stabilized in these patients. This demonstrates that good cognitive function is compromised when blood–brain barrier strength is compromised (which occurs when there is chronic inflammation in the body and brain).[8]

Other research indicates that a B12 deficiency can lead to brain shrinkage. Lower B12 status markers correlated with not only total brain volume but also global cognitive function. This is why B12 deficiency in the aging population is associated with high rates of dementia and cognitive decline, and possibly also Alzheimer's disease.[9]

Vitamin B12 is also needed to produce the protective lining around nerves known as the myelin sheath. Demyelination of that sheath occurs in diseases such as multiple sclerosis and other degenerative neurological conditions. Given that the myelin sheath is involved in nerve impulse signals traveling from one nerve to another, it follows that if that structure is weak, nerve signaling will be compromised. This can manifest as memory loss, difficulty with focus/concentration, word-finding difficulties, and slurred speech.

Frankincense Essential Oil

I have been utilizing essential oils more and more with my patients, and seeing great results. Essential oils, being lipid-soluble, can cross the blood–brain barrier easily and have good penetration into cells overall.

There are a number of constituents that make particular oils good for neurological symptoms. Some of the key ones are sesquiterpenes, because of how easily they cross the blood–brain barrier. These help to oxygenate the tissues, reduce inflammation, and calm the nervous system. They can support the endocrine system and have analgesic effects. Some oils that are high in sesquiterpenes are cedarwood, frankincense, patchouli, vetiver, ginger, ylang-ylang, myrrh, *Helichrysum*, *Melissa*, and black pepper.

Frankincense in my view is the very best essential oil for Lyme brain. So long as the highest-quality oils are used, frankincense can safely be taken internally. I have patients either put it directly under the tongue, or swallow it as a capsule or in some cases on the roof of the mouth (preferably toward the back of the mouth at the soft palate). Frankincense can also be put on the soles of the feet; the soles are a good entry point for essential oils, as the skin is quite thin, and yet the pores are the largest there of anywhere on the body, so systemic absorption is rapid and effective. Yet others apply it on the temples or the base of the skull.

Patients love frankincense – it helps with brain fog, focus/concentration, and emotional balance. I have a handful of patients who have seizurelike activity that is now controlled with daily use of frankincense. I have many more who report that their brains are so much clearer since using frankincense.

Acetyl-L-Carnitine

Acetyl-L-carnitine has long been used for brain and cognitive support, and there is much research supporting its use and benefit. It is much more absorbable than regular L-carnitine, and the acetyl-L form has superior blood–brain barrier penetration, which is desirable for those needing help with Lyme brain.

There are several mechanisms by which acetyl-L-carnitine helps the brain. It is a nutrient that helps to produce energy, thus fueling the cells, boosting their metabolism and improving their function.[10]

It also helps to metabolize fat and cholesterol so that the brain does not get "clogged" with plaques and deposits. Acetyl-L-carnitine can help to prevent the buildup of amyloid plaque, which can contribute to cognitive decline. It boosts levels of brain-derived neurotrophic factor (BDNF), which helps to repair damaged cells and even produce new brain cells. Acetyl-L-carnitine boosts nerve transmission and supports nerve regeneration. It also helps to repair myelin sheaths, as well as any damage to the blood–brain barrier caused by toxins, inflammation, and so on. It does this by boosting the antioxidant enzymes that naturally protect the barrier from toxic stress. Since we know that inflammatory damage to the blood–brain barrier can contribute to cognitive issues, neurological degeneration, reduced learning, memory decline, and depression, acetyl-L-carnitine can help to offset

such damage and for this reason alone is an important nutrient.

In terms of neurotransmitters, we know that acetyl-L-carnitine supports acetylcholine. It also has been found to support dopamine levels and prevent the age-related decline of dopaminergic receptors.[11] Another study showed that acetyl-L-carnitine increased norepinephrine in the hippocampus and serotonin in the cortex. Supporting norepinephrine and serotonin in the brain can help with depressive symptoms as well as cognitive deficits.[12]

Acetyl-L-carnitine may be one of the most important nutrients for the brain, given that it boosts metabolism, acts as a neuroprotectant, helps the integrity of both the blood–brain barrier and the myelin sheaths around nerves, and, perhaps most importantly, can repair already damaged nerve cells and structures, and promote creation of new, healthy ones.

Curcumin

Curcumin, a constituent of turmeric, has been used for centuries as an anti-inflammatory and antioxidant. It is also used in autoimmune issues to regulate immune function. There are many studies demonstrating its efficacy in reducing inflammation, and various mechanisms reported. One of the ways it reduces inflammation is by reducing pro-inflammatory cytokines that are found to be elevated in Lyme patients. As an antioxidant, curcumin has been found to increase levels of vitamins C and E, and prevent lipid peroxidation and oxidative damage.[13]

Equally beneficial for Lyme brain is evidence that curcumin can help regenerate and repair cells in the brain. Research shows that a component of turmeric known as aromatic-turmerone can increase neural stem cell growth in the brain by up to 80%.[14] Neural stem cells differentiate into various types of neurons – nice, new, healthy neurons! The study found that the number of actual stem cells produced increased with exposure to curcumin, and also that the stem cells increased the number of fully differentiated neural cells.

Curcumin may also be protective against various toxic metals such as copper and aluminum.[15,16] Certainly toxic metals are common in Lyme patients and can compound the effects of Lyme brain.

Curcumin has been found to enhance DHA levels in the brain. DHA is one of the vital fatty acids that support brain health – deficiencies have been linked to several cognitive disorders, including anxiety. DHA is either obtained through the diet or created from dietary precursors; however, the conversion rate from dietary precursors is low. Curcumin has been shown to increase conversion to DHA from the precursor alpha-linolenic acid.[17]

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Curcumin is a very safe and nontoxic substance with a good track record of success. It has multiple benefits – regulating the immune system, reducing inflammation, acting as a neuroprotective agent, and promoting neural regeneration.

Amino Acid Therapy

As we know, one of the contributing factors in Lyme brain is an imbalance in neurotransmitters, which can cause issues such as anxiety, depression, and problems with memory, cognition, and mental processing – really, all the things that we associate with Lyme brain.

Any neurological illness can deplete neurotransmitters. Neurological illness creates a higher need and demand for neurotransmitters, so there is a double-edged sword of increased need with depleted supply. Methylation defects also affect neurotransmitter production and utilization.

Amino acid therapy is a way to naturally and safely increase the supply of the raw materials that the body needs to produce neurotransmitters. We are supplementing with the building blocks so that the body can create more neurotransmitters for itself.

Each neurotransmitter has its own pathway and uses different amino acids.

The serotonin pathway starts with tryptophan and moves through 5-HTP to become serotonin. Interestingly, serotonin is converted to melatonin, so people with insomnia can also benefit from supporting the serotonin pathway.

I utilize 5-HTP extensively to support serotonin production. 5-HTP tends to be calming and balancing, and relieves depression.

The epinephrine pathway uses the amino acid phenylalanine, moving through tyrosine to become dopamine, norepinephrine, and epinephrine. Tyrosine in supplemental form is helpful for depression wherein there is extensive fatigue, low moods, apathy, low libido, and poor concentration and focus. I choose tyrosine when "the blahs" seem to be dominant in the depression picture, and 5-HTP more when feeling wired and anxious occurs along with it. Some people do well with both, but of course I recommend starting one at a time.

The GABA pathway starts with glutamine. However, in this particular case, we actually supplement with GABA itself. One reason for this is that it is available in supplement form as actual GABA, and also, while glutamine is an amino acid that can have some benefit in the brain, high glutamate is excitatory and causes more problems than it solves. Therefore to avoid the risk of too much glutamate actually opposing the desired result, a calmer brain, we supplement with GABA itself. I have found GABA to be most helpful for anxiety.

Amino acid therapy is a very safe way to support Lyme-brain recovery – it can lead to a more balanced and even mood, less depression and anxiety, better focus, and greater concentration.

Dr. Nicola McFadzean Ducharme is owner and medical director of RestorMedicine, an integrative medicine clinic based in San Diego, California. She has been treating Lyme patients for over 10 years using a combination of allopathic and naturopathic modalities. She is the author of *The Lyme Diet* and *The Beginner's Guide to Lyme Disease.*

Conclusion

These are just some of the modalities and supplements that I use to help with the cognitive and psychoemotional symptoms of Lyme disease. There are many others that can be helpful, and we didn't even get to touch on the dietary elements! My book, *Lyme Brain*, due for publication early 2016, will contain much more information on how to help. Sign up to be notified when the book is published at www.LymeBrainBook.com.

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Lithium: The Untold Story of the Magic Mineral That Charges Cell Phones and Preserves Memory

by James Greenblatt, MD, and Kayla Grossmann, RN

As far as cosmologists can tell, there were only three elements present when the universe was first formed some 13.8 billion years ago: hydrogen, helium, and lithium. As one of the three original elements, lithium is found throughout our atmosphere. The sun, stars, and meteorites burn brightly with the flame of this highly reactive element. On earth, lithium remains a major mineral component of granite rock, and also lingers in significant amounts in sea water, mineral springs, and soils. Lithium has also found its way into our cell phones, electric cars, and holiday fireworks. Every organ and tissue in the human body contains the mineral lithium, with particular importance in brain health.

Today, we do not tend to think of lithium as an essential mineral in human physiology and its critical use for expanding technology. Lithium does not evoke visions of stars, peaceful rivers, or strong, healthy bodies. Instead images of lithium are associated with pharmacies, doctor's offices, and back wards of psychiatric hospitals. Lithium is perceived, almost exclusively, as a dangerous drug used to treat severe mental illness with incapacitating side effects.

In a recent review in the *New York Times* titled "I Don't Believe in God, but I Believe in Lithium," author Jamie Lowe delivered a powerful testimony of her dramatic response to lithium – the drug that alleviated her mania and allowed her to live a normal, happy life. Her article also describes the kidney damage that has forced her to stop lithium and placed her on a waiting list for potential kidney transplant. She provides a unique insight into the life-changing prescriptive benefits of lithium, and the overwhelming fear she has of life without her lithium; a life without her sanity.

I have treated thousands of patients with similar backgrounds as Jamie's. This raised the question, how can a medicine provide such life-changing effects on mental health yet cause permanent damage to kidney and often thyroid function?

Twenty-five years ago, I attempted to answer this question by looking for the lowest dose of lithium that would alleviate symptoms. Rather than basing my prescription dosage on a number from a lab test that dictated a "therapeutic blood level," I listened to my patients. I began to see that patients on a lower dose of lithium – doses closer to the trace amounts found naturally in the environment – still experienced significant clinical results.

Psychiatry has much to learn from the untold story of one of its oldest drugs.

Lithium as Mineral

Lithium was given its official name by a Swedish chemist named Johan August Arfvedson in 1817. He isolated the element while studying petalite – a rich mineral deposit found in soils – on the remote island of Uto. The unique substance was named lithium after the Greek word *lithos*, meaning literally "from stone."

Just one year after its initial discovery, researchers noticed that there was something special about this new element. Lithium ore, when ground into a fine powder, turned flames a bright crimson color that intensified to a dazzling white when burning strongly. In addition to being highly reactive, the metal was also lightweight, malleable, and a good conductor of heat and electricity. These characteristics made lithium an immediately desirable commodity for industrial and manufacturing purposes. Since this time it has been used for manifold applications: in aircraft parts, fireworks, heat-resistant cookware, focal lenses, and even the fusion material in power plants. Today, the mineral is most commonly used for building the lithium-ion batteries that power our cell phones, tablets, laptops, and eco-friendly vehicles.

Over the past two centuries, scientists have gained a deeper appreciation of this alkali earth metal, which is now known to be relatively common in the earth's upper crust. As the 27th most abundant element, it can be found in rock sediments, salt

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flats, and mineral springs at varying concentrations throughout the globe. The largest deposits of lithium are salars, or vast saline basins in the deserts of South America. Lithium is also highly concentrated in clay beds and hard rock underground mines dotting Australia, China, and some parts of North America.

Lithium is in fact so ubiquitous in these environments that it can readily be found in food and water supplies. The US Environmental Protection Agency has estimated that the daily lithium intake of an average adult ranges from about 0.65 mg to 3 mg. Grains and vegetables serve as the primary sources of lithium in a standard diet, with animal byproducts such as eggs and milk providing the rest. Lithium has even been officially added to the World Health Organization's list of nutritionally essential trace elements alongside zinc, iodine, and others.

The most frequent source of lithium in the modern diet, however, is tap water. Depending on geographical location, drinking water contains substantial amounts of naturally occurring lithium. According to environmental surveys, water with high mineral content can translate to 2 mg or so of lithium per day.

There has been little research on the specific consequences of lithium deficiency in humans. However, trials in which animals have been put on low-lithium diets have revealed a gross decrease in reproductive function, lifespan, and lipid metabolism. It is quite possible that lithium deficiency has many other effects on human physiology, but the study of nutritional lithium has been overshadowed by the volatile reputation of high-dose pharmaceutical lithium.

Lithium as Medicine

Official documentation of the medical applications of lithium was first publicized by London doctor Alfred Baring Garrod, who used it to treat patients with gout. After discovering uric acid in the blood of his patients with gout, he wrote about pioneering the use of lithium in his 1859 treatise, *The Nature and Treatment of Gout and Rheumatic Gout*. Between the 1850s and 1890s, several other physicians experimented with lithium treatment because at the time uric acid was viewed as a critical factor in many diseases.

Both the medical literature and popular advertisements of the time abounded with praise for lithium. The Sears, Roebuck & Company Catalogue of 1908 advertised Schieffelin's Effervescent Lithia Tablets for a variety of uric acid afflictions. By 1907, The *Merck Index* listed 43 different medicinal preparations containing lithium. Even soft drink entrepreneur Charles Leiper Grigg understood that there was something special about lithium. In 1929, he unveiled a drink called Bib-Label Lithiated Lemon-Lime Soda with the slogan "It takes the ouch out of the grouch." Hailed for improving mood and curing hangovers, this product was eventually rechristened 7 Up. The "7" supposedly represents the rounded-up atomic weight of the element lithium (6.9), and the "Up" suggests its power to lift spirits. Lithium remained an ingredient of 7 Up until 1950.

An Australian psychiatrist, Dr. John Cade, is credited with first experimenting with high doses of lithium citrate and lithium carbonate as a treatment for manic depressive illness in 1949. He observed first in animals and then in human trials that lithium stabilized mood, restored memory, and improved cognitive function, even in his most challenging subjects. Because of his well-structured study and the dramatic results, some historians of medicine consider that Cade ushered in modern psychopharmacology.

Unfortunately, the timing of Cade's treatment successes was ill fated. The very same year, 1949, adverse reaction reports surfaced in the media about patients who were taking lithium chloride in the US. As physicians encouraged patients with heart disease and hypertension to avoid sodium chloride, lithium chloride was marketed as an alternative to sodium chloride in four different preparations: Salti-salt, Milosal, Foodsal, and Westsal. In the late 1940s and early 1950s, physicians around the country released reports of patients who developed lithium poisoning after they had used large, uncontrolled amounts of Westsal. Several deaths were also reported, leading the FDA to ban the use of lithium salt substitutes. "Stop using this dangerous poisoning at once!" exhorted the FDA. Lithium fell out of favor in the American medical community.

Despite this lithium chloride debacle, trials testing the efficacy of lithium carbonate for mania continued in Australia and France. Eventually the research from other countries became so compelling that by the end of the decade, a "lithium underground" had formed of US physicians prescribing lithium in the absence of official FDA approval. Finally, the FDA sanctioned lithium in 1970 as a new investigational drug for use in treatment of acute mania. By this time many other countries had already approved lithium, including France, the UK, Germany, and Italy. In 1974, lithium was finally approved to prevent recurrent mania.

Since the official FDA approval of pharmaceutical-dose lithium, the mineral has proved to be one of the most versatile and successful drugs in psychiatry. According to treatment guidelines, lithium carbonate is recognized as the first-line therapy in patients with bipolar disorder. Recent meta-analyses underscore the superiority of lithium as a prophylactic for both mania and depression. Lithium's effectiveness in suicide prevention has also been demonstrated. While antidepressants may treat depression, they often exacerbate symptoms of agitation, restlessness, irritability, and anger that can lead to impulsivity and aggression. Lithium, by contrast, has specific effects against suicide that are independent of mood stabilization. Substantial literature also exists to support the use of lithium in a broad spectrum of other neurological conditions including substance abuse, violent and aggressive behavior, ADHD, and cognitive decline.

The pharmacological mechanisms under which lithium operates have yet to be understood in totality, although many well-supported hypotheses exist. It appears that lithium functions in two central ways in the body's neurochemistry: repairing damaged neurons and stimulating neuronal growth. Proposed mechanisms for lithium's effect on balancing mood include the altering of dopamine, glutamate, and GABA levels in the synapses as well as modulation of secondary messenger pathways that effect neurotransmission, including the adenylyl cyclase system, cAMP signaling pathway, and phosphoinositide system. Accumulating evidence has shown that lithium's diverse neuroprotective actions involve direct changes in the expression of multiple genes.

It was once believed that genes were destiny. Scientists and clinicians held fast to the idea that a fixed genetic code was hardwired in humans at conception, and that mutations were a sure predictor of disease. However, it is now known that environmental factors have a profound influence on the ways in which genes are expressed. The study of epigenetics has revealed that lifestyle factors, including physical activity, learning, stress exposure, and pharmacological compounds, can essentially switch genes on or off. The mineral lithium is a powerful epigenetic factor. Key epigenetic mechanisms include histone modifications and changes in DNA methylation. Lithium works in both of these channels and has been shown to influence the expression of over 50 different genes. Working in these epigenetic pathways, lithium supports a wide range of neuroprotective and neurotrophic actions that literally change brain physiology.

Low-Dose Lithium

I believe that lithium is the most effective medication in psychiatry. Psychiatrists over the years have been hesitant to prescribe lithium because it is toxic at pharmaceutical doses. Concerns about side effects and toxicity are nonexistent when lithium is used as a nutritional, low-dose supplement. The untapped potential of low-dose lithium in psychiatry has implications for dramatically changing clinical practice with a safe, integrative strategy for the treatment of mental illness.

I have treated children as young as 4 years old and adults in their 70s with low-dose lithium. Here are a few examples of the hundreds of patients in whom this treatment has been successful.

A 4-year-old boy, Peter, had severe ADHD. Even at this young age, he was shunned by other children, and his parents were asked to remove him from preschool. It was easy to observe his aggressive behaviors in my office. A trace mineral analysis from a hair sample revealed no ➤

detectable lithium. I prescribed 250 mcg of lithium in liquid form. Peter's annoying aggressiveness diminished. He became able to make friends, and eventually he began to participate cooperatively with other children in a new preschool.

Shawn at age 8 was often in trouble for bullying. Although he had been diagnosed with ADHD, stimulants had not been helpful. His trace mineral analysis showed no detectable lithium. On 2 mg of lithium orotate, he showed significant improvement, and he lost interest in bullying other children.

A 20-year-old patient, Amy, was diagnosed with bipolar disorder. She had been doing better on Depakote, although she continued to have anger outbursts and uncontrolled rages. Although she had once been on prescription lithium, she had experienced side effects that prevented ongoing use. I prescribed 10 mg of lithium for her in conjunction with the Depakote. Her condition improved so much that she was able to leave a therapeutic boarding school to return home.

A middle-aged man named Brian made an appointment with me to talk about his problems with anger and irritability. I had no trouble imagining these problems, as I was unavoidably 15 minutes late in calling him to my office. He berated me for most of the session, and I later heard that he had been verbally abusive with my staff. Brian, I learned, had suffered from depression and was currently taking an antidepressant, but his irritability remained. His wife reported that his road rage escalated to such intensity that he would get out of the car and yell at other drivers. I added 10 mg of lithium to Brian's antidepressant treatment. Both he and his wife later reported that his simmering road rage subsided to nothing more than mild frustration.

The case of my patient Patricia was revealing by all of my assessment strategies: clinical history, family history, and trace mineral analysis. A 43-year-old therapist, she had been diagnosed at age 18 with depression and alcohol abuse. I learned from her story that her family of origin was deeply impaired by alcoholism. Patricia had been taking an antidepressant and had worked hard at maintaining her sobriety for 10 years. She came to me for enhanced support, as she complained that she was a "dry drunk," clinging to "white-knuckle sobriety." She felt chronically irritable. Trace mineral analysis revealed some level of lithium in her hair, but it was low.

Six weeks after I prescribed 5 mg of lithium, Patricia came to my office in tears. She was partly joyful that she no longer felt a constant level of irritability, but she also realized with regret what it must have been like for her family to have tolerated her irritability and anger for such a long time.

In an effort to organize and disseminate the information of low-dose lithium, I have started to compile additional case studies and ongoing research efforts on the website www.lowdoselithium.org.

In 1970, one research study analyzed levels of organically derived lithium in the water of 27 Texan counties and compared them to the incidence of admissions and readmissions for psychoses, neuroses, and personality disorders at local state mental hospitals. Data from a 2-year period were collected and analyzed. The authors noticed a marked trend: the higher the lithium content in the water supply, the lower the rate of psychiatric illness in that county. This association remained significant even after correcting for possible confounding variables such as population density and distance to the nearest state hospitals.

A follow-up study in the same Texan counties looked at similar variables over a longer 9-year span. Researchers came up with almost identical results: the incidences of suicide, homicide, and rape were significantly higher in counties where drinking water contained little or no lithium, versus those with levels ranging from 70 to 170 mcg/L. Unsure if these striking findings were somehow unique to that geographical region, other researchers have sought to replicate the study template in other areas throughout the globe. Lithium water studies have now been repeated internationally at sites in Austria, England, Greece, and Japan. Overall the collection has revealed a strong inverse correlation between aggressive crime and suicide and supplemental levels of lithium in the water supply.

Another interesting finding came from a study that looked at lithium levels in the hair of criminals. Trace mineral hair analysis is one of the most accurate methods for testing long-term mineral status and is therefore highly advantageous for determining where deficiencies are present. This study found that violent criminals had little to no stores of lithium when tested via hair mineral analysis, bringing forth the idea that perhaps lithium *deficiency* was contributing to oppositional and aggressive behaviors.

The most fascinating research recently, however, has been on the use of lithium for Alzheimer's disease. Given its being the only cause of death in the top 10 in America that cannot be prevented, cured, or slowed, researchers are spending billions of dollars on Alzheimer's disease. There is a fast-growing community of researchers suggesting that lithium may provide significant benefits in the treatment and prevention of Alzheimer's.

Lithium has been shown to disrupt the key enzyme responsible for the development of amyloid plaques and neurofibrillary tangles associated with Alzheimer's disease. This enzyme is glycogen synthase kinase-3 (GSK-3), a serine/threonine protein kinase that is important in neural growth and development. Notably, specific levels of GSK-3 are required to carry out the synaptic remodeling that drives memory formation.

In Alzheimer's disease, GSK-3 becomes hyperactive in the areas of the brain controlling memory and behavior, including the hippocampus and frontal cortex. This upregulation spurs GSK-3 to phosphorylate, or activate, amyloid-B and tau proteins in the neurons of these regions at an

aberrantly high rate. Over time these proteins accumulate to create the signature plaques and neurofibrillary tangles that disrupt the brain tissue and result in symptoms of cognitive decline. Lithium works as a direct GSK-3 inhibitor to prevent this overexpression, halting inappropriate amyloid production and the hyperphosphorylation of tau proteins before they impair brain function.

In addition to protecting the brain from the development of plaques and tangles, lithium has been shown to *repair* existing damages brought about by Alzheimer's disease pathogenesis. Lithium ions, for example, encourage the synthesis and release of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which in turn stimulate the growth and repair of neurons. Patients on lithium have been found to have significantly higher gray matter volumes in the brain. One study has even directly demonstrated that damaged nerve cells exposed to lithium respond with increases in dendritic number and length.

In a recent trial published in *Current Alzheimer's Research*, a nutritional dose of just 300 mcg of lithium was administered to Alzheimer's patients for 15 months. When compared with the control, those on low-dose lithium showed significant improvements in cognitive markers after just 3 months of treatment. Furthermore, these protective effects appeared to strengthen as the study proceeded, with many of the lithium-treated individuals showing marked cognitive improvements by the end of the trial. These results suggest that lithium could be a viable treatment for Alzheimer's disease when used at low doses over the long term.

Dr. Nassir Ghaemi, one of the more notable and respected advocates of lithium use in the medical community, recently published a review in 2014 in *Australian and New Zealand Journal of Psychiatry* summarizing the benefits of low-dose lithium therapy. Ghaemi and his colleagues performed a systematic review of 24 clinical, epidemiological, and biological reports that assessed standard or low-dose lithium for dementia along with other behavioral or medical benefits. Five of the seven epidemiological studies established a correlation with standard-dose lithium therapy and low dementia rates, while four other randomized clinical trials demonstrated that low-dose lithium yielded more benefit for patients with Alzheimer's dementia versus placebo. Based on these findings, Ghaemi stressed that "lithium is, by far, the most proven drug to keep neurons alive, in animals and in humans, consistently and with many replicated studies."

The Future of Lithium

Recognizing that nutrition is key to brain health is a fundamental premise of integrative medicine. Instead of focusing on just one type of intervention, integrative medicine tries to address all factors that may contribute to a mental disorder – bringing together nutritional supplements, medicines, psychotherapy, and lifestyle changes.

Lithium must be recognized as a critical component of nutritional assessments. Lithium is an underused nutritional supplement. The diverse neuroprotective mechanisms are truly remarkable. The scientific literature has shown that lithium modulates GSK-3, enhances the release of neurotrophic factors such as BDNF, and promotes epigenetic changes that resets the trajectory of mental illness. Lithium is powerful, reliable, cost effective, and, at low doses, completely safe.

With low-dose lithium, we have a safe nutritional supplement that is effective in treating a wide range of disabling symptoms of mental illness. Perhaps in the future, patients like Jamie Lowe, the author of the *New York Times* article, will not be forced to make a decision between mental and physical health. The compelling and growing scientific literature on the benefits of low-dose lithium therapy combined with over 25 years of clinical practice have convinced me that with low-dose lithium, it is entirely possible to have both.

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Find out more about their upcoming book and work on www.lowdoselithium.org.

Identifying Early Signs of Neurodegeneration

Datis Kharrazian, DHSc, DC, MS, MNeuroSci, FACN, CNS

Based on an interview with Nancy Faass, MSW, MPH

Health care providers are currently seeing an explosion in the incidence of gluten ataxia, early dementia, Parkinson's, and aberrant brain function with no clear diagnosis. It is vitally important that we identify symptoms of neurodegeneration at the earliest possible stage while there is still time to address them.

In integrative practice, treatment of the brain has generally emphasized "fix the metabolism and give high-quality supplements," assuming that alone will improve brain health. However, simply giving nutritional supplements cannot repair brain degeneration, because nutrients do not cause neurons to connect. By way of example, if a patient's arm is in a cast and the muscles atrophy, the patient will not be able to regain the strength or size of those muscles just by taking supplements; they must use the arm. Similarly, nutritional supplementation as the sole intervention has limited effect on neuroplasticity. When the brain begins to degenerate, our patients must engage in activities that make a difference in brain health.

Functional Diagnostics

The clinical examination starts the minute the appointment begins. If a patient is chronically late, for example, that is clinically diagnostic and raises a number of relevant questions:

- Why were they late?
- Did they get lost? Do they get lost all the time?
- Are they so bad with directions that someone had to drive them to the appointment?
- How long did it take them for them to fill out the new-patient forms? Did it take them three times as long as the average patient?
- How is their handwriting? Is it barely legible? Has it been declining?
- Were they able to remember important details when you took their history?
- Was their thinking disorganized? Did they constantly get lost in the timeline or backtrack?

Most people assume that these signs and symptoms are a natural part of aging. It is our task to help them realize that they should take these symptoms seriously and make the commitment to reverse brain aging.

Brain-Based Fatigue or Metabolic Fatigue? It is vital to differentiate brain-based fatigue from metabolic fatigue. Fatigue that originates in the brain results from tasks that require cognitive processing such as driving, working at the computer, or holding a focused conversation. Has the patient's attention span been impacted? Do they need coffee to stay alert? Were they exhausted by the trip to the office or the effort required to provide their medical history? These are all signs of early neurodegeneration.

Metabolic fatigue, on the other hand, is suspected when patients feel as if they cannot get out of bed and are tired all day. Practitioners tend to blame such symptoms on food sensitivities, overburdened adrenals, or impaired endocrine function, such as an underactive thyroid. However, loss of brain endurance should raise questions about cognitive functioning, indicating the need for a focused evaluation.

Ruling Out Disease

In assessing patients with neurodegeneration, the next step is to rule out the two primary neurodegenerative disorders, dementia and Parkinson's. If the patient does not have either of these pathologies, then we assess overall brain health. While they may not have symptoms of disease, they may still be subject to increased risk of neurological degeneration. Perhaps they cannot speak as clearly, or their coordination or balance is off. These are indicators of generalized brain degeneration rather than a specific disease pattern.

Dementia. Once we identify brain fatigue, we want to understand which areas of the brain have lost functioning. I use a questionnaire that I developed for Apex Energetics, which asks questions such as:

- Do you have loss of memory?
- Do you have difficulty finding words?
- Do you forget your keys all the time or where you put your phone?
- Do you forget phone numbers that you used to be able to remember?

These are also signs of early dementia. Most people are shocked to learn that many of these common symptoms are stage 3 on the dementia scale of the American Alzheimer's Association. Unfortunately, the impact of dementia on a person's life is not truly apparent until they reach stage 4. It is important to take trivial memory issues seriously and intervene if a patient's symptoms are worsening.

Parkinson's Disease. Patients with Parkinson's exhibit distinctive symptoms. They typically seem disinterested and are not very interactive. They present with a masked face, have a tendency to stare and blink very little, appearing expressionless. They are not being rude. In reality, they have lost facial tone and muscle activity due to neurological changes that are early signs of Parkinson's.

Although we associate tremors with Parkinson's, tremors occur only in the last stages of Parkinson's, once atrophy has occurred. Early indicators of motor impairment include walking slowly or shuffling, lack of arm swing when walking, or swinging just one arm. These patients also tend to lose good bowel function. Joint stiffness is frequently a chief complaint in Parkinson's. Patients have shoulder or hip problems that no one is able to fix and that tend to worsen. Chiropractic care or massage for a hip or shoulder condition brings only temporary relief as the problem returns immediately, another indicator of Parkinson's disease.

Gluten Ataxia. Another neurodegenerative disorder that is important to mention is gluten-based ataxia, which is growing in prevalence due to cross-reactivity to modern wheat and certain other foods. Symptoms usually involve dizziness, balance problems, or instability. Patients with ataxia tend to get carsick or seasick fairly quickly, and they can become nauseous if there is too much movement in their visual field.

During the exam, observe them walking. Can they walk in a straight line with their arms at their sides and with their eyes closed for more than three steps? If they cannot, that is a clinical sign of ataxia. Ataxia that is not related to head trauma or degenerative disease of the brain is described as *sporadic idiopathic ataxia*. The most common cause of this phenomenon is gluten sensitivity. These individuals need to be checked for both gluten sensitivity and neurological antibodies to cerebellar, GAD, and other markers, for proper diagnosis.

Identifying Causal Factors

Generally speaking, the initial goal in brain treatment is to identify the mechanisms that are involved. Are any of the following disorders factors in the patient's deteriorating brain health:

- Blood sugar imbalance (hypoglycemia, insulin resistance, or diabetes)
- Poor circulation and insufficient blood flow and oxygen delivery to the brain
- Brain inflammation
- Gut-brain axis dysfunction such as leaky gut
- A breached blood-brain barrier
- Neurological autoimmunity
- Insufficient basic nutrients and fatty acids
- Hormone imbalance
- Imbalanced neurochemistry
- Toxic exposure
- Chronic, debilitating stress
- A history of traumatic brain injury that is now starting to catch up with the patient

These are the factors that most commonly initiate neurodegeneration. For example, people with cold hands and feet typically have poor circulation and insufficient blood flow to the brain. When these individuals exercise or drink coffee, their brain function improves dramatically. Strategies to improve brain circulation include the use of botanicals, increased physical activity, and mental exercises to increase nerve connectivity. This type of approach makes it possible to intervene quite specifically with different mechanisms to slow brain degeneration.

Functional Assessment

In my practice I use a form that I developed for Apex Energetics, the *Brain Function Assessment Form* (BFAF), which is also available in a course I developed called *Mastering Brain Chemistry*. The assessment lists major symptoms specific to different areas of the brain, which helps to identify the locus of neurodegeneration. With this information, the clinician can intervene to increase activity in the area of the brain implicated, which is a basic rehabilitation concept.

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Early Signs of Neurodegeneration

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Functional Signs and Symptoms of Neurodegeneration

Frontal Cortex Impairment	
• Depression • Mental sluggishness and laziness • Decreased amplitude, slower movement • Poor impulse control • Poor social behavior and judgment • Impaired executive functions such as decision-making	• Poor handwriting • Poor cognitive function, such as math or planning skills • Poor cognitive learning • Poor muscle-coordinated learning such as dancing and playing sports • Poor recall
Temporal Lobe Impairment	**Parietal Lobe Impairment**
• Poor memory • Difficulty hearing with background noise • Episodes of tinnitus • Abnormal shifts of fatigue throughout the day • Ongoing episodes of insomnia	• Feeling unstable in darkness or with thick or high-heeled shoes • Unable to recognize objects through touch • Difficulty perceiving where one's limbs are • Becoming prone to falls and sprains
Cerebellum Impairment	**Occipital Lobe Impairment**
• Episodes of dizziness or vertigo • Nausea from visual input such as car or sea sickness • Poor balance • Subtle shaking at the end stage of movement	• Difficulty processing visual information and recognizing shapes and colors • Visual hallucinations or floaters • Visual persistence or reoccurrence of an image after it has been removed

Screening Tools. Simple screening exercises can be surprisingly useful in diagnostics:

- To screen patients (or yourself) quickly for brain function, give them five random words or a phone number to remember. Engage in conversation for a period of time so they are distracted. Then see if they can recall the exact words or the phone number. If they cannot, that is an early sign of dementia.
- Another exercise involves bringing the thumb and forefingers of each hand together very quickly, as fast as they can. If they are doing it slowly, that is an early clinical sign of Parkinson's.
- As mentioned, have the patient close their eyes and try to walk in a straight line. If they cannot take more than three steps, that could be one of the early signs of cerebellar ataxia or cerebellar degenerative disease, such as gluten intolerance, which is very common.

Obviously, a more comprehensive evaluation is needed to confirm a diagnosis, but these types of exercises serve to raise a red flag.

Hands-On Experience. Every year I teach a brain dissection course at Bastyr University. Students palpate brain tissue to identify degenerative changes and correlate them with the patient's health history. In some cases there is evidence of general overall brain degeneration; in other cases, there is brain degeneration in only one area. Surprisingly, it is rare for us to examine a brain that does not show any signs of degeneration. There is always degeneration; it is simply a matter of where and how much. The risk of dementia is now a battle that we all face, but one that most people ignore.

Advances in Lab Testing

Blood-Brain Barrier Integrity. An intact blood-brain barrier is another important aspect of brain health. We know that traumatic brain injury breaks down this barrier. Other factors that cause breaching of the blood-brain barrier include celiac disease, chronic gut inflammation, leaky gut syndrome, elevated homocysteine, and alcohol addiction. These disorders also increase one's susceptibility to inflammatory autoimmune reactions. Consequently, anyone with brain impairment should have their markers tested to determine whether their blood-brain barrier is intact.

When the blood-brain barrier is breached, the brain's immune cells react, producing antibodies in response. A test for these blood-brain barrier antibodies is now available through Cyrex Laboratories (Array 20), based on the work of Aristo Vojdani, PhD. Through his research, Dr. Vojdani has identified the specific protein sequence that antibodies take when the blood-brain barrier is breached.

If this antibody test comes back positive, the next step is to identify the mechanism(s) causing breaching of the blood-brain barrier. Is there a history of a previous head trauma, an ongoing inflammatory condition, gluten sensitivity, or some other dynamic? As a clinician your goal is find the cause(s), and then treat it. After one to two

months you will want to repeat the test again to determine whether the levels have changed. This is a clinical strategy similar to that used in the leaky gut model.

Gluten Sensitivity. Another lab test critical for people with neurological symptoms is the gluten-sensitivity panel from Cyrex, Array 3. Most clinicians are not fully aware of the enormous increase in the prevalence of gluten sensitivity and its relationship to neurodegeneration. We are now seeing many, many people with gluten ataxia.

We know that gluten antibodies can cross-react with brain tissue. When this occurs, the immune system is mistaking brain tissue for gluten, because these tissues are similar in structure. When the gluten-sensitive person consumes gluten, the immune system recognizes the gluten as an inflammatory trigger and produces antibodies that attach to gluten proteins. Once the gluten protein is broken down, the reaction stops. However, researchers have found that gluten antibodies can also attach to brain tissue, targeting it for destruction by the immune system. A specific example is the attachment of these antibodies to the protein synapsin in the cerebellum. The literature indicates that we can screen for gluten reactions in the brain by testing for antibodies to the enzyme transglutaminase 6. However, current tests for gluten sensitivity and for celiac disease typically check only transglutaminase 2, which indicates reactions in the gut. Cyrex Labs' test for gluten sensitivity (Array 3) also measures the brain-associated marker, transglutaminase 6.

Why is it so important to measure transglutaminase 6? The majority of reactions to gluten are neurological, rather than intestinal. In fact, recent research has found that two-thirds of the individuals who have an immune reaction to gluten have no gastrointestinal symptoms. Researchers hypothesize that gluten sensitivity is more of an immunological disease of the brain than a disorder of the intestine. Although gastroenterologists were the first to report gluten reactivity, the majority of gluten reactions take place in the brain.

The theory is that hybridized wheat, which researchers describe as "modern wheat," causes this reactivity. This is not to be confused with GMO wheat. Compared to native wheat, hybridized wheat is more protein dense, contains approximately 500 times more gluten, and includes proteins that are new to humanity. Research has found that some patients with these sensitivities react to hybridized wheat, but not native wheat. We also know that pesticides bind to the proteins of the wheat, changing the very nature of the proteins.

A study published in 2010 evaluated blood samples from 50,000 air force personnel that had been collected and frozen 50 years previously. These blood bank samples were compared with 10,000 gender-matched, age-controlled samples from air force personnel taken at the time of the study. The results showed a dramatic increase in gluten sensitivity and celiac disease. This finding is not an anomaly. The theory is that the hybridization of wheat and the binding of wheat proteins with pesticides explain the rise in immune reactivity.

Furthermore, gluten immune reactivity can also trigger molecular mimicry in the brain, a condition in which the immune system mistakes brain tissue for gluten, attacking the brain when gluten is consumed. Consequently, modern wheat can also cause massive inflammatory reactions in brain tissue and initiate neurological autoimmunity in some individuals, with devastating consequences.

Autoimmune Reactivity. Currently, the most common impairment in brain function associated with gluten sensitivity is cerebellar ataxia. In some cases, patients with sporadic ataxia and gluten sensitivity show dramatic improvement once they eliminate gluten. However, other patients do not improve, which has motivated additional research. Working in collaboration with Dr. Aristo Vojdani, we performed detailed testing for molecular mimicry in the cerebellum. To further study gluten sensitivity, we obtained monoclonal antibodies for different target sites in the cerebellum, such as GAD 65 and GAD 66. The defining characteristic of a monoclonal antibody is that it will only attach to a single antigen, unless the new protein is almost identical, referred to as molecular mimicry.

We then processed 220 foods, extracted the pure protein, and tested those foods to explore the hypothesis that other foods in addition to wheat can cross-react with tissue in the cerebellum. We identified approximately 40 foods that can cross-react with the cerebellum just as gluten does. Not everyone has antibodies to these 40 foods. However, some of this reactivity is quite common. For example, we found that peanuts can bind to cerebellum tissue. If one has a sensitivity to peanuts, antibodies could be elevated by the exposure. The antibodies attach to cerebellum target sites, which can result in cerebellum degeneration. We also found that in sensitive individuals, this type of reactivity can occur with other common foods as well, such as mustard seeds, the primary ingredient in mustard.

This understanding is changing the way we treat these issues clinically. We now perform routine testing for cross-reactive foods for all patients who have neurodegeneration. Just recently a patient was found to react to one of these cross-reactive foods, and when it was removed from the diet, that made a significant difference.

Once someone begins to develop autoimmune symptoms, particularly in the brain, other immune reactions can occur as well. The process involves more than just gluten as a trigger of neurodegenerative changes. Array 10 from Cyrex serves as a comprehensive food allergy test to evaluate patients for cross-reactivity.

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Rehabilitation

When practitioners learn and apply these simple strategies, we see life transformations take place. Strategies to modulate the immune system and support brain health include:

- The use of botanicals to increase blood flow to the brain
- Taking flavonoids to reduce neuroinflammation
- Consistently stabilizing blood sugar levels
- Removing food items from the diet that trigger sensitivity

Exercise. The single most important intervention to slow brain degeneration is, quite simply, exercise. A few minutes of physical exercise each day changes the chemistry of the brain profoundly. As little as four minutes of high intensity exercise daily raises the heart rate, dramatically increasing BDNF (brain-derived neurotrophic factor). This is a neurochemical that enables neurons to connect, increasing neuroplasticity. Simply jumping rope or running for ten minutes can have a profound effect, reducing the risk of dementia and saving the brain.

Sleep. Getting adequate sleep can also prevent brain atrophy. This is another very general, practical step we all can take to protect our brains.

Nutrients. Good nutrition and dietary factors create a more optimum environment for plasticity.

Sensory-Based Therapies. To maintain neuroplasticity, one must activate neurons through stimulation. When we recommend yoga, massage, manipulation, or biofeedback, these therapies are effective in part because they activate different receptors in the body, whether those are muscle spindles or Golgi tendons. When these receptors are activated, they fire to neurons in the brain, and as a result, promote neuroplasticity. Thus sensory-based treatments can have a beneficial impact on brain health.

However, to achieve the desired improvement, it is important to match the therapy to the area of function that needs support. It is not uncommon for a patient who has, for example, temporal lobe olfactory degeneration to benefit from aroma therapy. The patient may have a phenomenal outcome and refer friends to aroma therapy. However, if their friends have no functional degeneration in the olfactory region of the brain, the therapy may have no effect.

Mental Stimulation. Ultimately, the most effective therapy is a combination of physical receptor-based treatments (for example, yoga or massage) and other forms of stimulation. At the end of the day it is a matter of being both physically active and stimulating cognitive functions, to be both a scholar and an athlete. In addition to exercise, this could mean reading, performing arts, or painting. The goal is to achieve a receptor effect in the brain that goes beyond the effect of nutritional supplements alone. In the past we thought taking fish oil was enough to improve brain health. It is not.

Addressing Loss of Function. Treatment is a matter of understanding brain function and knowing which therapy activates the areas of the brain that most need intervention. The basic concept is "Whatever you cannot do, do that." If the patient is bad at math, then have them do math puzzle games. If they are really bad at drawing, then have them draw. If the patient's handwriting is terrible, they should work on their handwriting. That is the simplest way to teach this strategy without getting too complicated. When the patient's handwriting is deteriorating, the areas of the brain that exert motor control are degenerating. When they lose the ability to do math, their left frontal cortex is degenerating. When they lose their sense of direction, their parietal temporal lobe is degenerating. When they can no longer walk down a flight of stairs without holding the handrail, the cerebellum is degenerating. This is not a personality issue, it is not a matter of aging, it is neurodegeneration. This is not something we should get used to. We need to take these symptoms seriously.

Insight for Health Care Practitioners

I see practitioners who attend every seminar, constantly studying in order to help their patients, but that is only half of the equation. The other side of that issue is retaining all that information, which depends on brain health. Health care practitioners have to remember they are only as good as their brain function. Once brain function begins to deteriorate, it does not matter how many degrees they have or how much education they have; they are not going to be able to serve their patients.

We all lose neurons every year but we can still maintain a high level of function if we keep our brains active through physical and mental exercise. If we do not take brain health seriously, and we do not have sufficient neuroplasticity, then we begin to lose physical or cognitive skills, memory, or balance.

Once practitioners become educated about the prevalence of early-onset dementia, they realize how much trouble they could be in. They see that the symptoms they have neglected in themselves could be quite serious. If practitioners do not save their own brains, no one else is going to. When we teach the course we say, "We know you're here for your patients, but we really want this course to be about you."

Datis Kharrazian, DHSc, DC, MS, MNeuroSci, FACN, DACBN, DACNB, CNS

Dr. Kharrazian works as a clinician, researcher, professor, industry consultant, and author striving to incorporate the most up-to-date, evidence-based concepts into clinical practice and to investigate unanswered clinical questions through his research. He serves as associate clinical professor for the Department of Preventive Medicine at Loma Linda University School of Medicine, and adjunct professor at the National University of Health Sciences and at Bastyr University. A faculty member of the Institute for Functional Medicine (IFM), he participates in program development for IFM. He has also served as a trainer and educator in functional medicine and nutrition, having personally trained several thousand health care providers in post-graduate seminars over the last 15 years. Dr. Kharrazian recently completed a post-doctorate clinical research scholar program at Harvard Medical School. He has published scientific papers in the fields of nutrition, autoimmunity, and toxicology, and is involved in research on autoimmune molecular mimicry and environmentally induced immune reactivity. In his private practice he sees patients seeking non-pharmaceutical alternatives to manage chronic conditions through diet, nutrition, and lifestyle applications. His practice has up to a one-year waiting list and is limited to patients suffering from chronic health conditions. As a researcher and clinician, Dr. Kharrazian shares his clinical model in his two best-selling books, *Why Do I Still Have Thyroid Symptoms When My Lab Test Are Normal?* and *Why Isn't My Brain Working?*

Resources

Book. *Why Isn't My Brain Working?* This highly readable book is appropriate for both consumers and professionals. A comprehensive resource, the book contains 21 chapters, each focused on a different mechanism that can impact brain degeneration and cause neurological symptoms. The work is 587 pages, with more than a thousand references, and includes case histories, clear explanations, and clinical action steps. A copy of the book's table of contents and associated resources are available online at www.BrainHealthBook.com and on Amazon.com.

Online Course for Consumers. This course, entitled *One-to-One: Save Your Brain – A Six-Week Rescue Plan*, will take viewers through the same steps Dr. Kharrazian takes with his patients to begin repairing brain health and function. To get on a waiting list for this online class, visit www.DrKNews.com/one-to-one.

Course on Functional Neurology. A 20-hour course on neurology will be offered this year by the International Association of Functional Neurology and Rehabilitation. The course will cover neurological exams, selection and interpretation of lab work, and the development of individualized plans for brain rehabilitation. Live case histories on video are included, with before and after interviews, and clinical specifics such as lab work. Additional information will be posted on the association's website at: www.iafnr.org.

Course on Neurochemistry. Apex Seminars offers a course designed by Dr. Kharrazian, *Mastering Brain Chemistry*, available to licensed health care professionals. The course is approved by the University of Bridgeport and provides CEUs for acupuncturists, chiropractors, naturopaths, nutritionists, and nurses (but not currently CME units). For further information, see: www.ApexSeminars.com.

Laboratory Testing. Cyrex Laboratories, located in Phoenix, AZ, offers a series of test panels for the detection of gluten sensitivity (Array 3), cross-reactivity (Array 4), autoimmune mechanisms (Arrays 5, 7, and 8), and blood-brain barrier integrity (Array 20). Descriptions of Cyrex tests and arrays can be found at www.CyrexLabs.com.

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The Gut Microbiome: Your Mood's Micromanager?

by Filomena Trindade, MD, MPH, and Megan Murphy, CAP

All disease begins in the gut.
– Hippocrates

In today's world we are hyperconnected yet ironically lonelier, more disconnected, and unhappier than ever. Mood disorders are at unprecedented highs (Qureshi & Al-Bedah 2013). Depression haunts 18.8 million Americans, most of whom are women. Every day, the relentless plague of anxiety torments 19 million adults in the US. This means that about 1 in every 10 people is afflicted with depression and/or anxiety. Depression will affect 1 in 4 women in their 40s or 50s and is now the leading cause of disability worldwide (Perlmutter 2015). In spite of the alarming prevalence of mood disorders, they are still socially stigmatized. The societal expectation to "hold it together" has left many cases of clinical depression untreated due to shame, embarrassment, or denial of symptoms. For the US economy, these cases of depression are a serious concern because they carry a hefty price tag of over $50 billion spent annually. These numbers are much higher than the costs for treatment of complicated, life-threatening illnesses such as heart disease or AIDS. Depression and anxiety are clearly no small matters of concern and are well deserving of our keen and earnest consideration.

Depression and anxiety can't be identified and diagnosed on the basis of a single laboratory exam alone. Depression, for example, doesn't lend itself exclusively to any one particular biomarker. Therefore, clinicians typically use laboratory testing to rule out other serious conditions that can sometimes mimic the symptoms of depression. Then, if laboratory values appear in the normal range and the symptoms are persistent, the diagnosis matching the patient's qualitative experience becomes "major depressive disorder" (MDD), also known as clinical depression, major depression, or unipolar depression. MDD is a mental illness characterized by episodes of all-encompassing low mood, accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities.

Treatment and Prognosis of Mood Disorders

No matter how mild or severe the case of depression or anxiety, standard-of-care treatment is consistently prescription medication. The tools that doctors use to handle cases of mood disorders are most commonly selective serotonin reuptake inhibitors (SSRIs) such as Prozac, followed by serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants, and in recalcitrant cases, monoamine oxidase inhibitors (MAOIs). Strong benzodiazepines such as Xanax are used for persistent anxiety, and in many cases, practitioners prescribe additional, adjunct anti-inflammatory, antiulcerant, cholesterol-reducing, and antihypertensive drugs in conjunction with these potent anxiolytics and antidepressants in an effort to manage or suppress symptoms. Doctors are hard pressed to suppress symptoms and control physiology.

If patients do not respond to any of the aforementioned interventions within eight weeks, then they wind up with a diagnosis of treatment resistant depression (TRD). About one-fourth to one-third of patients with MDD do not respond adequately to two or more prescribed antidepressants (US Department of Health and Human Services 2012). TRD is associated with an overall worse prognosis and higher medical costs. To manage this type of resistant depression, the *American Family Physician* recommends an algorithm of consecutively rotating different classes of antidepressants (Little 2009). The problem is that this model fundamentally dismisses the root causes of MDD and/or TRD. It aims to suppress symptoms with progressively stronger psychoactive drugs or steadily higher doses of the same drug. Unfortunately, this strategy often leaves patients overly medicated and uncomfortable from the myriad of side effects stemming from their complicated psychotropic cocktail. The presence of mood disorders such as depression and anxiety does not mean that there is an inherent deficiency in Prozac or lack of adequate Xanax in a person. Quite the opposite; it means that there is a hidden, underlying physiological mechanism causing the patient's neurochemistry to go awry. This invariably makes interventions such as psychopharmaceuticals nothing more than a Band-Aid, and it brings into question the effectiveness of our standard of care.

'Uprooting' Mood Disorders: A Functional Medicine Approach

If we want to truly alleviate the suffering of those with serious depression and anxiety, we can't keep looking at masking or suppressing the symptoms alone. As clinicians, we have to start asking ourselves, why? We need to find the root cause(s) of the symptoms if we want to provide our patients with lasting relief. Any good gardener knows that if you want to get rid of weeds, you have to take them up by their roots; trimming down the stalks will only strengthen their hold in the ground. The same is true with the body. If we don't address the root cause(s) of dysfunction, then improvement in symptoms will be superficial and fleeting at best.

Figuring out the root cause of mood disorders often means doing some heavy-duty detective work. We have to find the common thread that links all of the patient's seemingly unrelated symptoms. We might ask ourselves, what could peripheral symptoms such as constipation or bloating have to do with my patient's chief complaint of anxiety or depression? When we're looking at the whole of the patient's symptomatology and not just at isolated components of their physical or mental health, we begin to "connect the dots," so to speak. Often there is a keystone problem within one bodily system, such as the gastrointestinal (GI) tract for instance, which can catalyze imbalances in other areas of the body, such as the central nervous system. This is the kind of systemwide domino effect that we have to keep our eyes out for.

Every system in the body exists in functional relationship with one another. That is why we have to critically consider the entirety of the patient's health in every respect, until we can confidently identify the impetus for their depression. This means using all of our tools – a detailed physical examination along side with a thorough investigation of the patient's history. Following the identification and elimination of the root cause(s) of the mood disorder, we find that the patient's symptoms miraculously diminish and their condition is no longer "resistant." In actuality, it is entirely receptive to treatment, needing only for the root cause(s) to be removed. The reason for this lies in the fact that the origin of mood disorders rests in a disruption of the functional integrity of one or more physiological processes. Hence, once that integrity is restored, symptoms are alleviated and finally we see lasting results.

Mood Disorders and Stress

As we begin to probe deeper into the question of what could be causing the disturbances in brain chemistry that are characteristic of mood disorders, we may first want to consider the ubiquitous presence of stress in our modern lifestyle. One of the most powerful contributors to depression and anxiety is simply everyday chronic stress. While the acute stress response can be an asset for raising performance levels during critical events, if stress becomes persistent and low-level, all parts of the body's stress apparatus (the brain, heart, lungs, vessels, and muscles) become chronically over- or underactivated. This may produce physical or psychological damage over time. In fact, almost all illness is caused by stress, aggravated by stress, or in itself stress-inducing. Stress is implicated in up to 95% of all primary care visits in the US (NIOSH 2006). That's because as stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, it causes deleterious effects in numerous organ systems. These changes in themselves can directly incite mood disorders when prolonged over time. Anxiety and depression can also be spawned indirectly by the downstream effects of stress. For example, cortisol-induced intestinal barrier dysfunction can trigger a local inflammatory response characterized by the production cytokines, which travel to the brain and create detrimental changes in mood (Loftis et al. 2010; Söderholm & Perdue 2001). Therefore, clinically, it is crucial to consider the possibility that stress could indeed be at the root of many cases of the mood disorders that we see today.

Mood Disorders as Multifactorial

Every patient has a unique and complex history which catalyzes the progression of their symptoms into a mood disorder. Although the presentation of depression or anxiety could be identical between two different patients, the pathogenesis of their symptoms may be entirely different. There are a myriad of possible offenders in the development of mood disorders, each of which is worthy of its own review depending upon the particular case. Additionally, each potential contending cause may not single-handedly induce anxiety or depression by its own accord. Often we see that there are a multiple of confounding factors in the development and progression of mood disorders. Therefore, it is of the utmost importance that the clinician take responsibility to retrieve the patient's full history, untangle the web of causality, and connect the dots so that they can determine the root cause(s). Table 1 is a small list of some of the most common physiological factors predisposing a person to mood disorders.

Table 1: Precipitating Factors for Mood Disorders

Gut bugs: Dysbiosis and the gut microbiota
Food allergies/sensitivities
Digestive insufficiencies/excess
Oxidative stress/mitochondrial dysfunction
Stress-psychological or physical or both
Hormone imbalance
Toxins
Nutrient deficiencies
Prescription medications
Inflammation
Genetic predispositions/SNPs
Infections
EMFs and dirty electricity
Trauma – pyschosocial or physical
More than one cause?

As you can see, anxiety and depression are not "just in the head." Most often, they are symptoms of a greater, systemic, physiological imbalance. The dysfunction of any number of organ systems in the body may provoke neurochemical imbalances which then have the

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capacity to induce mood disorders. In this article we will focus on one particular area of interest in the body that has recently garnered a substantial amount of emerging research: the gut–brain axis (GBA). Specifically, we will investigate the relationship between the microbiome in the gastrointestinal tract, its relationship with the central nervous system, and the resulting impact on mood.

The Gut–Brain Connection

In recent years, the gut has earned the affectionate title of "second brain." It warrants this kind of headline in part because of its ability to manufacture a physical reaction from an emotional stimulus. We are all familiar with the feeling of being "sick to our stomach" when we hear bad news or getting "butterflies" when thinking about kissing a lover. These are examples of how the gut becomes the physical expression of our mental-emotional state; and, as we will soon come to see, it is also the mental-emotional expression of our physical state. Moreover, the so called "second brain" is an actual physical, anatomical structure. It is a large plexus of nerves called the enteric nervous system (ENS) which indeed operates much like a second brain. It can function entirely independently from the central nervous system (CNS) and rivals none other than the spinal cord in pure quantity of nervous tissue. The ENS is a subconsciously driven mechanism that not only regulates entire digestive process but also, as it turns out, asserts its own form of communication with the CNS.

We've known for a long time that the CNS communicates with the gut. For instance, in the face of stress, the brain and spinal cord make the executive decision to shut off digestive function and shunt resources to more vital, survival physiological processes such as increasing heart and respiration rates. However, recent research published in multiple journals has made it strikingly clear that the reverse is true as well. The gut also talks to the brain.

The communication between the gut and the brain is bidirectional – a two-way street with equal amounts of traffic heading in *both* directions. If we pay attention, our clinical experience often confirms this. Namely, "Psychiatric comorbidity, including depression and anxiety, occurs frequently in up to 60% of all patients with a functional gastrointestinal disorder" (Park et al. 2013). One study even showed that patients with irritable bowel syndrome (IBS) had stark physical changes that occurred in the brain – alterations in the cingulate gyrus, cortical thinning, and enhanced glutamate signaling (Labus et al. 2014); and, what's more, visceral hypersensitivity accompanied these changes in neuroanatomy and physiology. Moreover, given the nature of this poignant relationship between the gut and the brain, it should be no surprise that the induction of chronic depression alters motor activity and the microbial profile in the colon (Park et al. 2013). And it doesn't stop there. The feedback between the gut and the brain goes full circle. Under the influence of a neuropsychiatric condition, indicators from the GI tract travel to the brain to affect its functioning and subsequently, the changes in brain function feed back to the gut to alter the motility, secretion, and immunological response of the intestines (Fichna & Storr 2012). To close the loop, these changes in the gut link back up to the brain, and symptomatically we see the perpetuation of the already disordered mood.

As you can see, the circular feedback between the gut and the brain is so intimate that their roles in regulating the stability of mood blur into one another. The functioning of the gut and the brain seem to work more as a singular continuum rather than two discrete organ systems. In fact, clinically, it is often difficult to delineate which factor – the gut or the brain – first initiated pathogenesis. We're faced a causal dilemma, as in which came first, the chicken or the egg? Regardless of the instigator, however, it is imperative that treatment for mood disorders factor in both sides of this intricate GBA.

Gut–brain axis is the term used to refer to the two-way communication between the gut and the CNS. Fichna and Storr, in their July 2012 article in *Frontiers in Pharmacology*, detail the major players in the GBA as the ENS, the gut wall in the periphery (including the microbiota), the CNS, and the HPA axis. All these constituents of the GBA work to pass messages back and forth between the gut and the brain by using various signaling molecules. These messengers travel along neural, endocrine, and neuroimmune pathways. Holzer and his team did an amazing job of simplifying this concept in their article in *Neuropeptides* 2012. They explained that the gut talks to the brain via four different information carriers: (1) sensory neurons – both vagal and spinal afferent neurons, (2) cytokines, (3) gut hormones, and (4) gut microbiota-derived signaling molecules. These molecules manage to transmit information from deep within the gut and disseminate it all the way to the brain. Then, the other way around, the brain talks to the gut via autonomic neurons and neuroendocrine factors. These brain-to-gut communication vehicles carry outputs stemming from the CNS and going to the intestines. Therefore, the term *gut–brain axis* encompasses all of these bidirectional signaling molecules that travel endlessly between these two seemingly unrelated parts of the body.

Stress, Leaky Gut, and the GBA

A range of factors, all of which seem to be associated with systemic inflammation, appear to increase the risk for developing depression. Possible precipitating factors include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental caries, as well as a deficiency in sleep and vitamin D. In this article however, we will focus on the distinct role of intestinal permeability as a source for inflammation and as a causative factor underlying the dysfunction of the GBA and the consequent effect on mood.

The mucosal membrane of the intestines is made up of epithelial cells that function to digest and absorb nutrients, regulate immune response, and mount a barrier that separates the internal lumen of the gut from the external environment. Under normal circumstances, this wall of cells is sewn together by tight junctions which are selectively permeable to only a relatively few molecules. However, because the intestinal mucosa is sensitive to neurohormonal signals emitted from the CNS, it is subject to the tyranny of stress. In fact, "various types of psychological and physical stress induce dysfunction of the intestinal barrier, resulting in enhanced uptake of potentially noxious material (e.g., antigens, toxins, and other pro-inflammatory molecules) from the gut lumen" (Söderholm & Perdue 2001). It appears that when the body is inundated with a stressor, autonomic nervous stimulation causes the release of corticotrophin-releasing hormone (CRH) and/or acetylcholine at nerve fibers adjacent to the intestinal barrier. These neurotransmitters then go on to activate nearby mast cells that are speculated to release the bioactive constituents ultimately responsible for inducing epithelial permeability (Söderholm & Perdue 2011). In other words, following a stressor, neuroendocrine factors such as acetylcholine and CRH could be the instigators for the breakdown of tight junctions between intestinal epithelial cells. Given the onset of stress, the functional integrity of the intestinal barrier is substantially compromised and we see an increase in gut permeability.

We often think of stress as purely psychological; however, it can be physical as well. If a patient has a hypersensitivity to foods containing the protein gluten for instance, they will produce IgG antibodies in response to the gliadin. This is a physical stressor because the IgG reaction triggers the overproduction of zonulin, which then loosens the tight junction barrier and increases the permeability of the gut wall (Karakuła-Juchnowicz et al. 2014). The immune system has to then respond to the presence of unmetabolized molecules seeping from the gut lumen out into the bloodstream. The risk of this "leaky gut" is that there is an increased load of antigens passing through the gut mucosa. This inevitably incites an inordinate level of immune stimulation and in the end leads to inflammation. Inflammation is a "pathway to both risk and neuroprogression in depression" (Berk et al. 2013).

Inflammation/Cytokine Theory of Depression

The question remains, how exactly does intestinal permeability and its resulting immune-inflammatory response affect the brain and precipitate a mood disorder? According to one theory, the answer is cytokines. Cytokines mediate between the immune system and the CNS. For instance, during the inflammatory response following an incident of gut barrier permeability, the brain intercepts these immunomodulatory signaling molecules known as cytokines. Cytokines switch "on" or "off" immune-regulating proteins such as interferons (IFN) and interleukins (IL). In their circulation, these pro-inflammatory, immune-stimulating cytokines exert their influence on the brain in four main ways: (1) via the vagal nerve, (2) by seeping through a weak and porous blood–brain barrier, (3) through active transport across the blood–brain barrier, and (4) in binding to endothelial brain cells (Loftis et al. 2010). Once they've accessed the brain, cytokines intercede in synaptic transmissions and can alter both the anatomical structure of neurons as well as their physiological functioning. In fact, chronic exposure to an excessive number of these molecules can even deteriorate neuroplasticity which is essential to healthy cognition, mood, and behavior (Loftis et al. 2010).

While it is postulated that cytokines are the intermediaries between an inflamed leaky gut and mood disorders, other studies have shown that they may also be behind the link between stress and depression. That's because cytokines ignite sympathetic arousal and HPA axis activation (Fichna & Storr 2012). Even as long ago as the mid 1990s, scientists correlated the presence of cytokines, levels of stress, and the severity of depression. Now, over the course of a decade more of research, the idea of a neuroimmune, potentially stress-related, cytokine-induced depression is central to our biological understanding of the disorder.

The Role of the Microbiota

At the same time that cytokines relay messages to the brain in the presence of inflammation in the gut, there is another highly influential mediator that must be considered in gut–brain communication: the gut microbiota (GM). A central player in the GBA, the GM consists of some 100 trillion bacteria with over 1000 different species, outnumbering human cells 10 to 100 times (Zhou & Foster 2015). As with any ecosystem, diversity in the GM is prized, and maintaining this well-balanced ratio of distinctive species may very well be our ticket to both physical and mental well-being (Park et al. 2013; Zhou & Foster 2015).

Interestingly enough, this vast internal ecosystem never looks exactly the same between any two people. As with fingerprints, we all have microbiomes that are uniquely characteristic (Zhou & Foster 2015). Even identical twins have variability in the constitution of their GMs (Simões et al. 2013). In a large part, the GM is a reflection of the environment to which we have been exposed since birth. The colonization and diversity of microbes in our gut are influenced by our mother's method of delivery (vaginal or C-section); whether we were breast fed; our first solid foods; if we grew up with siblings; what kind of diet and lifestyle we've had to date; whether we travel frequently or have used many antibiotics in the past; as well as our genetics, sex, and age (Tillisch 2014, Zhou & Foster 2015). The GM unmistakably interfaces with our environment and adapts accordingly. It coevolves alongside us in dynamic

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participation with the multitude of changes that we encounter throughout our lives.

Research suggests that we host this array of commensal bacteria because we have a symbiotic, mutually beneficial relationship with them. They play an integral role in a variety of physiological processes that are critical to maintaining homeostasis. In return, we grant them free access to "room and board," giving them three square meals a day to enjoy in our perfectly warm, ideally anaerobic gastrointestinal (GI) tract. We are most obliged to house these little bugs because they happily take on a number of critical responsibilities important to the maintenance of our everyday health. Table 2 below enumerates the functions of the GM identified to date; although we know full well that this list will surely grow as more research is done and additional undertakings of the GM are discovered.

Table 2: Functions of the Microbiome

Modulation of host nutrition and energy harvest
- Digestion of carbohydrates and proteins
- Fermentation and breakdown of food components indigestible by the host for nutrient harvest

Affect signaling pathways influencing lipid and glucose metabolism

Development of host immune system and immune modulation

Protection against pathogens

Drug metabolism

Bile acids metabolism

Influence of intestinal epithelial homeostasis

Produce and secrete neurotransmitters

Production of vitamins

Absorption of minerals

Influences learning and memory

The role of the GM is many-sided and mutually interdependent with other bodily functions. Scientists speculate that the reason is that over the course of millions of years, the microbiome has coevolved in a give-and-take rapport with other systems such as the CNS, immune system, and endocrine system (Montiel-Castro et al.). If this is indeed true, we would find that an inadequate microbiome might be indicated in numerous pathologies, and in fact, it is. Subpar condition of the microbiota is associated with "neuropsychological disorders including depression and autism spectrum disorder, metabolic disorders such as obesity and gastrointestinal disorders including inflammatory bowel disease and irritable bowel syndrome" (Zhou & Foster 2015). We are only beginning to understand the breadth of influence that these microflora have in our bodies. What we do know, however, is that they appear to have an unexpected, profound, and far-reaching effect on the brain.

Introducing the Gut–Brain Axis

The GM may in fact be the single most influential component of the GBA. The two-way relationship between the microbiota and the CNS means that when there is a disruption in the constitution of microbes, brain chemistry and behavior can change (Mayer et al. 2015; Tillisch 2014). Vice versa, the proceedings of the brain can stimulate changes in the microbial constitution of the gut thereby effecting GI function such as motility and secretion (Park et al. 2013). The GM has a profound influence on the brain and can actually alter both its development and functioning, through the use of substances such as neurotransmitters, neuropeptides, cytokines, hormones, bacterial metabolites, and growth factors as well as the enteric neurons, vagal afferent nerves, and finally, immune and HPA axis modulation (Tillisch 2014; Fichna & Storr 2012; Zhou & Foster 2015). In the spirit of reciprocity, the CNS also uses some of the same routes of communication – the vagal nerve and HPA axis – to talk to the gut.

The vagus nerve is of particular interest in this discussion as it is the cranial nerve which innervates the GI tract and processes the bulk of autonomic parasympathetic stimuli. In fact, the "... bidirectional signaling between the gastrointestinal tract and the brain, mainly through the vagus nerve, the so called 'microbiota-gut-vagus-brain axis' is vital for maintaining homeostasis and it may be also involved in the etiology of several metabolic and mental dysfunctions/disorders" (Fichna & Storr 2012). Namely, the GM uses the vagal nerve to administer its remarkable influence on the CNS and the body at large, in part through the direct activation of neurons embedded in the gut lining.

The influence of the GM on this gut–brain feedback loop lies in its ability to mediate neuronal function of ENS neurons (Zhou & Foster 2015). It appears that the microflora actually depend on the ENS and vagal nerve to administer their effect through the GBA. Put another way, the GM itself may be able to activate neuronal pathways that then go on to influence the functioning of the CNS and, hence, the state of our mood. This particular pathway of the GBA was confirmed in a study done by Bravo et al. in 2011 in which the probiotic *Lactobacillus rhamnosus* was given to rats with both subdiphragmatic vagotomies and intact vagus nerves. After the microbial manipulation, the mice without the vagus nerve had no change in mood or behavior, whereas rats who maintained an intact vagal nerve had "reduced anxiety and depressive-like behaviors and long-term changes in gamma-aminobutyric acid receptor expression in the CNS" (Zhou & Foster 2015), specifically in the hippocampus, amygdala, and locus coeruleus (Tillisch 2014). In a similar manner, Bercik et al. (2010 and 2011) demonstrated that probiotic treatment can minimize anxiety induced by gut inflammation. These anxiolytic effects were associated with changes in brain-derived neurotrophic factor and were dependent on the vagus nerve.

According to Montiel-Castro et al. in their 2013 publication in *Frontiers in Integrative Neuroscience*, "The microbiota-gut-brain axis has multiple effects on emotions, motivation and other higher and complex cognitive functions ... [and] may even influence memory formation, emotional arousal, affective behaviors and decision

making processes." The microbial population in the gut can have this effect in part because of its relationship with the vagus nerve. Microbially stimulated vagal afferents send signals to the brainstem nuclei, as well as cholinergic and noradrenergic projections to the cortex – all of which end up mitigating emotional well-being, behavior, and cognition (Tillisch 2014). Numerous studies such as these have substantiated the role of the microbiota in triggering vagal afferents via enteric neurons which then signal the CNS and ultimately produce a change in mood.

Gut Microbiota in the Stress Response

The central nucleus of the amygdala is famous for being the emotional learning center and fear-processing locus of the brain. One fascinating study showed that signals from the amygdala can actually activate the HPA axis (Fichna & Storr 2012). This in turn causes a cascade of neuropeptides such as corticotrophin releasing factor (CRF) and adrenocorticotropic hormone (ACTH) along with glucocorticoids, to be disseminated. The flood of stress hormones spawns anxiety-type behaviors, undesirable changes in bowel habits, and visceral sensitivity (Fichna & Storr 2012). Furthermore, in the presence of a stressor and HPA axis activation, cortisol is released, which "...can alter gut permeability and barrier function, and thus contribute to variations in gut microbiota composition" (Montiel-Castrol et al. 2013). These findings demonstrate the link between emotional fear leading to stress and finally to GI sensitivity. This is important because this chain of events occurs by way of the HPA axis and the ENS – two central players in the GBA.

While a stress response initiated from the brain can disrupt the bowel, the state of the bowel's microbiota can also disrupt the stress response in the brain. In fact, it appears that the CNS depends on the microbiota to mediate the fear response. For instance, studies conducted on mice without adequate microbiota (germ-free mice) showed a disproportionate, inordinate stress response (Tillisch 2014). In the same way, another study on humans showed that with the addition of beneficial microbes, there were improvements in mood and a decrease in urinary cortisol levels (Tillisch 2014). Lastly, in yet another study, the effects of the commensal flora *Bifidobacterium infantis* were tested in newborn rats subjected to early life stress by being separated from their mothers and forced to swim. During the swim test, cytokine levels and markers of motivation and brain monoamines were measured. Amazingly, the results indicated that in spite of the stressors, the rats treated with the probiotic had scores similar to rodents that had never experienced any early life stressors. And what's more, they had a "normalization in brainstem noradrenaline and peripheral cytokines" (Tillisch 2014). In sum, all these studies demonstrate that the stress response can be mediated by beneficial gut microbes that seem to be able to quell the reactivity of the HPA axis. Indubitably, the stability of our stress response and thus our mood depends at least in part on the cross-communication between the trillions of bacteria that inhabit our gut and the CNS.

The Gut Microbiota in the Immune Response

The GM can also affect brain chemistry through immunomodulation. Gut microbes can trigger a local immune response at the level of the intestinal mucosa. This immune signaling often goes hand in hand with intestinal barrier dysfunction, ENS activation, and changes in GI sensory motor function (Tillisch 2014). In fact, it appears as though after the administration of probiotics, positive changes in the GM may "reduce inflammation, restore epithelial barrier function and potentially ameliorate behavioral symptoms associated in children with autism" (Zhou & Foster 2015). In the same vein, cognitive impairment due to diabetes and inflammation significantly improved after probiotic treatment in animal models (Tillisch 2104). In addition, by working through the immune system, the GM (including pre- and probiotic agents) can regulate the production and circulation of pro-inflammatory cytokines (Montiel-Castrol et al. 2013). And, as aforementioned, cytokines have significant effects on neural activity. For example, low-grade inflammation stemming from chronic infections in the GI tract can disrupt gut function and indirectly encourage anxiety and depressionlike behaviors; these changes in mood are likely "... immune-mediated, and involve changes in pro-inflammatory cytokines and altered metabolism of kynurenine/tryptophan pathways" (Borre et al. 2014). Again, we see the bidirectional nature of the GBA, and in this case the role of the gut microbiota in that communication, as a modulator of inflammatory cytokines. Naturally, all of these data make the human intestinal microbiome a keen area of interest for researchers hoping to discover how to ameliorate the outstanding rates of mood disorders that we see today.

The Gut Microbiota in Neuropsychology

One of the most fascinating aspects of the microbiome is that certain strains of bacteria can actually manufacture and secrete numerous neuroactive substances. Neurotransmitters such as gamma-aminobutyric acid, serotonin, catecholamines, and histamine can all be bacterially produced (Tillisch 2014; Dinan et al. 2013). These neurohormones can conduct their signals to the CNS with the help of local neuroendocrine cells on the gut epithelia (such as enterochromaffin cells) and/or through enteric nerves (Tillisch 2014). At the same time, the microbiota also influence the endocrine system by letting off "metabolites such as short chain fatty acids, biogenic amines, neurotransmitters and neurotransmitter precursors [that can] gain access to the systemic circulation" and later affect mood (Tillisch 2014). We speculate that it is likely that the metabolic byproducts of the microbiota depend

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in part on their strain and in part on the relative activation of the HPA axis and immune system. Clearly, the presence of the GM is an integral part of the inexorable gut–brain continuum and must therefore be aptly considered in the management of mood.

The Gut Microbiota in Nervous System Development

Along with the faculty of manufacturing neurotransmitters, the GM also appears to be influential in the actual development of the nervous tissue within the CNS and ENS. Studies on germ-free mice with no commensal bacteria show that "the myenteric plexus of the jejunum and ileum ... [had] an unorganized lattice-like appearance, with fewer ganglia and thinner nerve fibers" (Zhou & Foster 2015), as well as an abnormally developed HPA axis, among other things (Tillisch 2014). The functional consequences of these structural abnormalities cannot be underestimated. Germ-free mice experienced less brain-derived neurotrophic factor, an irregular stress response, as well as decreased intentional motility, immune function, and cell excitability (Zhou & Foster 2015; Tillisch 2014). Interestingly enough, however, after colonization with standard microbiota, many of these functional abnormalities were considerably rectified. This result demonstrates both the pliability and significance of the GM in the GBA.

The Gut Microbiota and Diet

The GM may be the linking factor between diet and depression. Diet has been shown to affect the composition of the GM (Simões et al. 2013), and in the opposite direction, accumulating evidence indicates that the makeup of GM influences behavior. According to Jørgensen et al. (2014), a diet high in sucrose and poor-quality saturated fat contributes to depressionlike behavior in mice. In their study, mice fed a diet high in fat had adverse changes in both behavior and microbial composition. The underlying mechanism behind this may have been the documented increase in interleukins, cytokines, and TNF-alpha – all of which are participants in the inflammatory cytokine model of depression.

Additionally, food sensitivities causing an IgG reaction may affect the permeability of the gut and be another source of covert inflammation leading to depression (Karakuła-Juchnowicze al. 2014). As we have noted ad nauseam, the GM responds to a leaky gut with immune activation, often inciting inflammatory cytokines that ultimately prove to dysregulate mood. Together, this evidence suggests that the mediator between food and mood is indeed the GM.

Reconstituting the Gut Microbiome: A Frontier in Mood Management

There are innumerable factors in our modern diet and lifestyle that sabotage the balance and diversity of the ecosystem in our gut. Anything from infection, stress, antibiotics, and environmental toxins to depression, excess sugars, and poor-quality soil in conventional food sources could weaken the integrity of the GM. In the same vein, while basic hygiene is vitally important, our obsession with sanitization does not help our microbial diversity thrive. Antibacterial sprays and gels kill both the good and the bad bugs. As a result, our immune systems are left without a piece of their inborn GI defense, and we find ourselves getting sicker more often. Whether intentional or not, the aggregate effect of our war on microbes renders our baseline microbiome less than robust. Consequently, we become vulnerable to tenacious, opportunistic gut pathogens such as *Candida albicans*. In short, any type of intestinal dysbiosis has the potential to stimulate the GBA and lead brain chemistry awry, effectively subjecting us to the pain of anxiety and/or depression (Park et al. 2013).

While it may be difficult to keep dysbiosis at bay given the circumstances of our modern world, the good news is that, with more awareness, we can actively promote the status of beneficial bacteria in the gut. Researchers are optimistic that future therapeutic strategies for mood disorders may invoke the talents of the GM to harmonize the GBA with the intention of allaying anxiety and depression. With each passing day, the scientific community continues to grow in its understanding of the nature of the GM and its therapeutic potential. On that note, as you may have gathered from the previous discussion, each strain of intestinal bacteria has a different "personality," if you will. Specific microbes seem to impart certain advantageous or deleterious effects on the GBA, depending on their nature. It is our task, among others, to identify the tendencies and actions of these microbes in the body so that we are better able to harness their potential and target their therapeutic capability in clinical practice.

Until relatively recently, the majority of studies on the effects of probiotics on the microbiome have been done on rodent models. However, more recently one study in humans demonstrated that consumption of a fermented milk product containing a combination of probiotics (*Bifidobacterium animalis, Streptococcus thermophilus, Lactobacillus bulgaricus,* and *Lactococcus lactis*) actually modulated brain activity (Tillisch et al. 2013). In this study, social anxiety was measured after 4 weeks of eating this fermented food. What was found was " ... a reduction in brain activity in a network of areas, including sensory, prefrontal, and limbic regions, while processing negative emotional faces" (Hilimire et al. 2015). In other words, the participants had less reactivity to negative social stimuli after regular ingestion of probiotics than they had done before. Furthermore, a control group that ingested a nonfermented milk product showed no such changes in brain activity. This suggests that the probiotics in the fermented milk were responsible for the modulation in brain activity that reduced social anxiety. Hence, probiotics could possibly be used as a low-risk intervention for the treatment of anxiety (Hilimire et al. 2015).

We also have data suggesting that the anxiety often associated

with chronic fatigue syndrome can be mediated by the ingestion of probiotics. Measurements on the Beck Anxiety Inventory starkly decreased after regular consumption of *Lactobacillus casei*. Similarly, in a double-blind, placebo-controlled trial, the effects of *L. helveticus* and *B. longum* were measured on healthy participants. At the end of 30 days of consuming these beneficial bugs, participants reported substantially less psychological distress (Zhou & Foster 2015). Another study of the same caliber demonstrated that prebiotics or "trans-galactooligosaccharide[s], which promote the growth of indigenous beneficial gut bacteria such as *Lactobacilli*, resulted in decreased scores on the anxiety subscale of the Hospital Depression and Anxiety Scale (HADS-A) in patients with irritable bowel syndrome" (Hilimire et al. 2015). Cumulatively, these evidences support the idea that mood is regulated, at least in part, by gut bugs.

It is quite possible that one day, instead of going to the doctor and getting a prescription drug for anxiety or depression, psychiatric patients may very well receive "psychomicrobiotics" instead (Fond et al. 2015). These individually targeted psychotropic microbes would be aimed to work through the GBA to relieve symptoms of a mood disorder. With the use of stool testing, it is indeed possible that a snapshot of an individual's unique microbiome could be assessed and subsequently assigned the appropriate psychomicrobiotics. Manipulating the microflora to combat microbial dysbiosis in psychiatric patients can be done through the use of probiotic or prebiotic supplementation and/or by fecal microbial transplant. The addition of beneficial bacteria can "influence end-points related to mood state (glycemic control, oxidative status, uremic toxins), brain function (functional magnetic resonance imaging fMRI), and mental outlook (depression, anxiety)" (Bercik et al. 2014). In sum, as the field of gastrobiological psychiatry grows, we see the increasing relevance of the GM as an access point from which to therapeutically direct the proceedings of the GBA and correct a disturbance in mood.

Finally, while this article has focused on the role of the GM in mood disorders, it is important to remember that anxiety and depression are complex, multifaceted issues with numerous possible etiological factors. That being said, given the substantial evidence that the GM works through the GBA to either catalyze or ameliorate mood disorders, it is imperative that clinicians thoroughly investigate this mechanism as a possible contributor to their patients' disease, as well as a potential pathway to their long-term healing and recovery.

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Defining the Cannabis Revolution

by Stephen Holt, MD, DSc

Distinguished Professor of Medicine (Emeritus)
Consultant to the Cannabis Industry

The Evolving Use of Cannabis

The increasing availability and support for the use of cannabis present important issues of medical, economic, social, legal, and political significance. These challenging events form the basis of the "cannabis revolution" which has accelerated in its progression in recent times. As cannabis creeps toward the status of national legalization in the US, many people are attracted by its recreational use and medical treatment applications. As a consequence, a burgeoning cannabis industry is taking shape, but this industry is not always operating like the ethical pharmaceutical or nutraceutical industries.

Many people argue that the corporate culture of the cannabis industry will have to change and consolidation appears to be inevitable. Decisions to legalize or prohibit cannabis (marijuana) use in the US have triggered endless debates. These arguments are becoming somewhat futile as the US further evolves with the inevitable legalization and decriminalization of marijuana use. At the time of this writing, there has been legalization of cannabis for recreational use in the states of Colorado and Washington. This expanded use of marijuana has emerged with an increasing recognition of the medical benefits of cannabis.[1-6] These benefits are hard to dismiss and impossible to deny.[5,6]

Current federal laws regulating cannabis use amount to a circumstance of "prohibition." These federal regulations are increasingly perceived as "behind the times" due to their incorrect definition of cannabis as a drug without medical benefits. President Barack Obama has indicated that legislation and regulation of cannabis use should occur at the state level of government. Accusations have been made that these circumstances are a "cop-out" by the federal government. At the time of this writing, there are a couple dozen states that have passed legislation for the use of medical marijuana. This circumstance is creating some degree of confusion as each state legalizes cannabis with some differences in legislation and certain parochial restrictions.

The absence of consensus opinions on precise indications for the medical applications of cannabis may lead to different future legislation and regulations in some states.[5,7] At present, there is room for the potential clash of state legislation and federal government policy. Regulatory agencies run by the federal government have found themselves between "a rock and a hard place." However, signs are developing that the federal government is "backing off" or acting like a "crocodile with no teeth." A solution to these pending problems would be widespread acceptance of revised federal legislation that could be defined for cannabis legalization. However, this potential approach has been the subject of much disagreement, and it is unlikely to occur in the near future.

The former widespread "prohibition" of cannabis (marijuana) use as a result of the 1937 Marijuana Tax Act has led to an unfortunate lack of scientific studies on the biological actions of the many components of the cannabis plant and their effects on health and well-being.[7] Up until about a decade ago, 90% of all cannabis research focused on the negative outcome of cannabis use.[5,7] Furthermore, a significant number of people have accused regulatory officials of "standing in the way of cannabis research," even in recent times. There are some anticipated needs for change in the ever-evolving regulations concerning marijuana use. Political and legal systems will be challenged by some of these changes. Arguably, politicians should not be making unaided "medical decisions" about indications for cannabis use. That said, widespread concerns exist about the current lack of knowledge about cannabis science among the health-care professions. This situation is compounded by shameful inertia in the planning of medical education on the science and application of cannabis.

The emerging landscape of the use of cannabis presents "information overload" for many people, including medical professionals.[8] Rapid political reforms have created some degree of misunderstanding and confusion among the general public. Such misunderstandings could affect the responsible use of herbal cannabis and related products. Therefore, urgent and widespread education is required on how society should apply the psychoactive and medicinal effects of marijuana. This education is necessary to ensure cannabis use in a safe and responsible manner. It is clear that the Internet is playing a role in shaping

the use of cannabis, but a significant portion of on-line (Internet) information about marijuana is inaccurate, biased, and sometimes incorrect. This situation hampers the broadcast of valid information to help guide the public on the use of cannabis. Moreover, illegal cannabislike products (synthetic pot) with major toxicity concerns are available for sale on the Internet.

The "cannabis revolution" has mounting support among the general public. For example, the Pew Research Center undertook a survey (March 2013) of the public support for medical cannabis legalization. This survey indicated that 52% of the public favored cannabis legalization versus 45% against legalization. It is apparent that there have been significant increases in the number of Americans who support marijuana legalization over the past few years, and current estimates are that 58% of the population of the US may favor medical cannabis legalization. While widespread support for medical cannabis use is growing fast, significant reluctance to support the legalization of cannabis for recreational purposes persists.

Pandora's Box Has Opened

When it comes to the recreational and medical use of cannabis (marijuana), Pandora's box has opened, or is opening, in many locations in the US. All that remains in the box is "hope." "Hoping" for positive consequences of these circumstances, many people seem to be satisfied with current legislative changes, but some have shown disinterest, and several groups have formed to protest and stop further approvals of its availability. With cannabis legalization there are changes in the frequency of cannabis use and its selected composition with preferred types of cannabis that favor the use of high potency cannabis (rich in THC [tetrahydrocannabinol]).

One need not be blessed with the talent of a visionary to appreciate that greater strides in legalization and decriminalization of marijuana are "around the corner." A principal feature of the "hope" that remains in Pandora's box is an overriding desire to create circumstances that satisfy the dictum of Hippocrates: "Above all, do no harm."[1] Harmful consequences of cannabis use do exist, even though many people have considered these risks to be low. That said, most young people think that cannabis is quite safe. Moreover, cannabis can contribute in specific circumstances to "harm reduction" or "harm production." A key issue is the presence of harm that can occur in teenagers. Prevention strategies should be applied to these youngsters.

The Revolution

The cannabis revolution involves global advances and fundamental changes in the acceptance of marijuana use over the past decade and rather precipitous legislation in some places in the US to accept legalization of its use. Once subject to general prohibition, cannabis consumption has blossomed into circumstances of increasing acceptance and widespread consumption with a "dual status" (legal or illicit). Depending on where people live in the US, cannabis is still viewed in a confusing manner as a legal or illicit drug.

Cannabis use is accompanied by a fundamental change in how many people think about this complex natural drug concoction (produced by the plant *Cannabis sativa*). I reiterate that major factors in its increasing popularity are the perceptions that marijuana is safe or even innocuous. Safety issues remain the basis of occasional ferocious debates among some politicians and scientists, but general opinions of safety have emerged. Perhaps it is more relevant to think about degrees of safety of use that are context specific. Furthermore, the emotional index on cannabis use by consumers is often "high," especially for compassionate use in palliative care and for children with severe epilepsy. Like it or not, the electorate has tilted toward support for cannabis use.

The DEA's Position on Cannabis

The Drug Enforcement Agency of the US (DEA) makes it clear that it does not recognize marijuana smoke as a medicine. Its negative opinions focus on smoking cannabis, which it describes as unsafe and having "not withstood the rigors of science." The DEA has stated that it "will vigorously enforce the CSA (Controlled Substances Act) against individuals and organizations that possess, manufacture or distribute marijuana for recreational use, even if such activities are permitted under state law."

I conclude my position statements by emphasizing the current and growing enigma of disagreement between state and federal government laws. While medical legalization of cannabis proceeds without apparent federal opposition, the federal government stands firm on its antimarijuana opinions. In further articles, I shall summarize aspects of the ongoing cannabis revolution.[9]

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Field Control Therapy and Successful Treatment of a Variety of Brain Disorders

by Savely Yurkovsky, MD

> Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter, as well as our sorrows, pains, griefs and tears. Through it, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant. ...The same thing makes us mad or delirious, dreadful and fearful, whether by night or by day, brings sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness. These things that we suffer all come from the brain, when it is not healthy ... and the tongue speaks in accordance with the things seen and heard on any occasion. But when the brain is still, a man can think properly.
>
> – Hippocrates

While the above quote says it all about the direct relationship between our quality of life and function of the brain, the sad fact of modern life is that the human brain is rapidly becoming an endangered species. Epidemics of autism and ADHD, Alzheimer's and multiple sclerosis, depression and anxiety, bipolar and OCD, insomnia and migraines, drug addictions and suicide, all support this tenet and one of the serious deficiencies in its prevailing treatments. The main reasons for the failure of treatments is that these attempt to correct brain chemistry gone astray, dopamine, serotonin, or other, while being unable to address the more important primary sources of these chemical imbalances. These are the corresponding brain zones and their true causes of abnormal functioning. In the process, such neurotransmitter or other balancing treatments not only treat virtual shadows of disease, instead of its very root cause, but also lead to loss of valuable time and allow these causes to continue inflicting deeper brain damage. The end result, as our sad statistics confirm, are these epidemics and also "wonder drugs" causing chemical dependency, drug addiction, and even suicides.

The Field Control Therapy (FCT) approach presented here is based on a different area of neuroscience that focuses on the primary regulatory structures of the brain and how to enter and collect the necessary information directly from these and other internal organs, via bioresonance testing. The latter overcomes the major stumbling block in chronic diseases, which is the inability of all laboratory and imaging testing to identify the direct causes of diseases of the internal organs. The treatment is homeopathic, involving a proper combination of isodes, or energetic copies of toxic substances and infectious agents, as well as sarcodes, or energetic copies of the internal organs.

Since one picture indeed is worth 1000 words, presented below is the medical picture of patients themselves who have been treated with FCT.

Patient S. G.

Man in his 60s with a lifelong history of bipolar disorder, which necessitated 15 hospitalizations. He is a former user of marijuana and LSD. Mental and physical fatigue, brain fog, and insomnia were other complaints. Certain foods, computer, any stress and especially undertaking projects would produce mental problems, particularly mania with nonstop talking and complete sleeplessness. Past treatments by an alternative psychiatrist did not help.

Bioresonance testing findings over the course of the treatment. Silver amalgam, mercury, lead, residues of marijuana, LSD, and antibiotics; parasitic and yeast infections, EMF radiation, all affecting the brain directly or indirectly.

FCT homeopathic treatment and addressing EMF problems. He received the corresponding homeopathic sarcodes of the affected areas of the brain and other organs, and of the causative agents responsible. Also, several classical constitutional homeopathic remedies for deep-seated genetic predisposition, Lachesis, Sulphur, and Argentum nitricum. He also acquired very effective protective Memon technology to reduce pathological effects of EMF radiation from his house, car, cell phone, and computer on his brain and body.

Outcome. Bipolar disorder, fatigue, brain fog, and chronic insomnia are

long gone. Being a very dutiful person, he gets occasionally distraught with some imposed responsibilities. For this he has recently received another homeopathic remedy.

Patient J. L.

"I think I would die from this," stated a middle-aged woman at her first visit, referring to her 24/7 anxiety, panic attacks, and depression, for 6 years. Fatigue and malfunctioning thyroid were other problems. Her prior alternative treatments had failed.

Bioresonance testing findings over the course of the treatment. Mercury, lead, Lyme, yeast and parasitic infections, EMF all affecting her brain limbic zone, which handles emotions, and also hypothalamus, pituitary, thyroid, adrenals, ovaries, and immune and gastrointestinal systems.

FCT homeopathic treatment and addressing EMF problems. She received the corresponding homeopathic sarcodes of the affected areas of the brain, and other organs, and of the causative agents responsible. She also acquired Memon technology in order to reduce the multiple pathological effects of EMF stress. It is of interest that when, at the earlier stage of her treatment, she started suddenly experiencing a return of palpitations and anxiety in her house, she intuitively checked her circuit breaker box with the Memon device. It so happened that it had been removed by an electrician shortly before. After she reinstalled it, her symptoms promptly subsided.

Outcome. A happy and energetic woman.

Patient R. K.

Man in his late 20s with depression, panic attacks, poor memory, insomnia, and brain fog for some dozen years. He had received numerous psychotropic drugs without success and was still consuming a few.

Bioresonance testing findings over the course of the treatment. Mercury, worms, Lyme disease, candidiasis, viral infection, and EMFs all having multisystemic effects, including his limbic zone and frontal lobe, which handles memory and clear thinking.

FCT homeopathic treatment and addressing EMF problem. He received the corresponding homeopathic sarcodes and isodes of the affected areas of the brain and other organs, and of the causative agents responsible. He also acquired Memon technology to reduce the multiple pathological effects of EMF radiation and its blocking impact on the treatment.

Outcome. After 7 treatments and being off psychotropic drugs for 4 months, he reported being free of all of his brain-related problems for the first time in 12 years. ➤

Field Control Therapy

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Patient N. D.

A patient in his 60s suffered from chronic depression, SAD, and early-stage Lou Gehrig's disease. Computer use worsened his depression and neurological symptoms.

Bioresonance testing findings over the course of the treatment. Mercury and other toxic metals, Lyme disease, and EMFs were all affecting his brain, peripheral nervous system, and other systems.

FCT homeopathic treatment and addressing EMF problem. He received the corresponding homeopathic sarcodes of the affected areas of the brain, spinal cord, nerves and other systems, and of the causative agents responsible. He also installed Memon technology in his house, office, car and computer in order to negate destructive effects of EMF radiation.

Outcome. Depression and SAD resolved to where he no longer needs his former mandatory spring breaks. Also, his neurologist removed the diagnosis of Lou Gehrig's disease.

Patient C. J.

A 9-year-old girl was referred to a psychiatrist for psychotropic medications because of the girl's restlessness, OCD, and unpredictable tantrums with aggression and depression. All of these were intensifying, in spite of therapy. Insomnia was another problem.

Bioresonance testing findings over the course of the treatment. Streptococcus A, worms and Lyme infections, mercury affecting her limbic zone, and EMFs affecting the pineal gland, which regulates sleep.

FCT homeopathic treatment and addressing EMF problems. She received remedies for her afflicted limbic zone and its causative agents. Memon was installed in the house to reduce EMF stress.

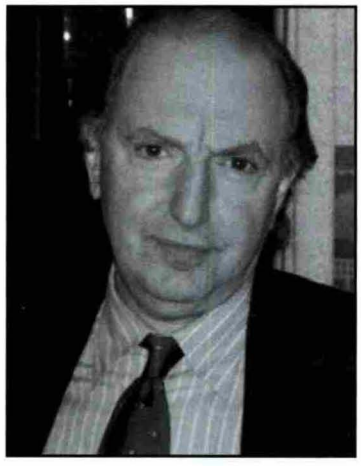
Outcome. She was completely cured in only two treatments; her mother described her daughter's response to the treatment as "huge and dramatic" and "she is just normal." Of note, C. J. was treated with antibiotics for Lyme disease at age 2 and was assumed, as it commonly is, to have recovered from it. While it is possible that she became reinfected with Lyme following antibiotics, I have never encountered, even among the few positive responders to pharmaceutical Lyme treatments, like her, anyone who has completely recovered from Lyme disease.

Conclusion

While the presented morbid findings such as mercury, candidiasis, parasites, or EMFs and others related to brain pathologies of these patients are not new, there are certain notable advantages in the ways that these have been addressed by this approach:

- the highly sensitive diagnosis via special bioresonance testing that can detect the causative agents and malfunctioned organs, before and after any treatments;
- their effective homeopathic treatment and, in the case of EMFs, effective protective devices;
- the safety of the treatment, which accounts for a high potential for an uncontrolled redistribution of mercury and other toxic metals in the body, during any detoxifying treatments.

One cannot overemphasize the importance of properly addressing EMF radiation, as this acts as the major blocking force in detoxification, immune resistance, and other vital functions. ◆



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

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

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

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

Dr. Yurkovsky's seminars on DVDs, devoted to autism, other brain disorders, and Lyme disease, serve as a virtual step-by-step textbook classic explaining the fundamental nature of all chronic diseases (available at www.yurkovsky.com). His book in progress explains the inevitability of the current epidemics of autism and numerous other brain and somatic diseases and how to solve them.

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

Epigenetics: Nature Meets Nurture in Psychiatry

by Jay Lombard, DO

Epigenetics is a biological process whereby the environment and experience influence and regulate the expression of the human genome. This discovery resolves the centuries-old nature/nurture debate about the primary effectors of our biological constitution and our ability to modify our inheritance. This is clearly relevant to how we address psychiatric disorders and brain plasticity, a biologically adaptive process that involves gene regulation via epigenetic factors. Our understanding of epigenetic biological mechanisms within the brain offers a promising new paradigm related to the pathophysiology of psychiatric disorders and the potential to address them at their root cause. Pharmacological and nonpharmacological treatments that target gene expression afford a novel opportunity to treat brain disorders that were once regarded as intractable.

The physical barrier to gene transcription occurs by restricting access to the underlying genomic DNA. Epigenetic regulation involves access to regulatory regions comprising histone-modifying enzymes at specific CpG sites. CpG sites are regions of DNA wherein a cytosine nucleotide becomes methylated through DNA methyltransferase enzymes which have the net effect of suppressing gene transcription. The attachment of a methyl group to cytosine is catalyzed by a family of enzymes known as DNA methyltransferases. About 60% to 75% of mammalian gene promoters reside within CpG islands, suggesting that these regions are the key regulatory sites of gene expression.[1]

The manipulation of these CpG islands through methylation or demethylation is instrumental in regulating gene expression for a number of processes in the brain, particularly the maintenance and consolidation of long-term memory.[2] Epigenetic control of DNA expression strengthens specific synaptic connections over others and is the specific mechanism whereby experience and environment can exert physical changes within the brain. In addition to methylation, epigenetic mechanisms that regulate gene transcription may also involve acetylation via histone acetyltransferases and histone deacetylases (HDACs), all of which act in a concerted fashion to determine the activity of a given gene. Histone acetyltransferases add acetyl groups causing the chromatin surrounding DNA to be in a relaxed state to promote gene expression. Conversely, histone deacetylases work by promoting transcriptional repression. There is substantial crosstalk between DNA methylation and histone modifications which involves interaction between DNA methyltransferase enzymes and histone-modifying enzymes.[3] As mentioned above, DNA can be methylated via DNA methyltransferases (DNMTs), which occur at CpG sites that repress gene activity. The carefully coordinated balance of methylation/demethylation as well as histone acetylation/deacetylation is what ultimately determines gene expression resulting from epigenetic environmental influences. It is precisely this balance that is required for synaptic changes that parallel long-term memory and changes in behavior.

Epigenetic gene modification has been shown to have very clear effects on the biology of brain processes. Changes in the levels of DNA methylation at specific CpG islands have been linked to genes which regulate the production and release of neurotransmitters and neurotrophic factors.[4] Most notably, hypermethylation of brain-derived neurotrophic factor (BDNF) with the net effect of reducing neurotrophic factors has been reported in several animal and human models of posttraumatic stress disorder (PTSD). For example, in animal models, stress-driven changes in DNA methylation of the BDNF gene has been observed in a rodent model of PTSD.[5]

Epigenetic regulation is crucial for normal brain development, and in addition to changes in the methylation of BDNF, there are a number of other important immune based and hormonal influences as well. Furthermore, there is an abundance of evidence that gene loci are differentially methylated between controls and psychiatric patients.[6] Neurodevelopmental disorders, such as autism, have been demonstrated to involve changes in miRNA expression and DNA methylation in hundreds of common and rare gene

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variants.[7] Recent studies suggest that schizophrenia may be characterized by aberrant DNA methylation, resulting in a deficit of coordinating epigenetic processes across promoter gene networks.[8] Clinical studies have found that childhood adversity and stressful life events in adulthood increase the risk for major depression.[9] The epigenetic basis for increased vulnerability may be based upon the observation that individuals with major depression exhibit greater DNA methylation and gene repression.[10] In abused suicide completers, the BDNF gene is hypermethylated compared with controls.[11] These results suggest that epigenetic changes in early childhood may significantly contribute to the neuropathology of depression by reducing the activity of neurotrophic factors.

While the importance of DNA methylation during development is well established, the role of DNA methylation-demethylation in the adult brain has only recently become appreciated in several pathological states, including drug addiction and PTSD. There are even some studies which suggest that epigenetic modifications can be transmitted to offspring, which raises the possibility that behavioral experience in adult life might influence gene expression in subsequent generations, a controversial concept known as transgenerational inheritance. Researchers have shown that higher levels of good maternal care cause the female offspring to show the same high-quality care toward their own offspring, validating the idea that behavioral phenotypes are socially transmitted from generation to generation through genetic factors that modify particular CpG islands.[12] Changes in the methylation status at a single CpG site in the glucocorticoid receptor have been linked to maternal grooming behavior in animals across generations.[13] In humans, the September 11 terrorist attacks in New York saw the detection of lower cortisol levels in the 1-year-old offspring who were gestating in utero at the time that their mothers witnessed the attacks, again demonstrating the profound effects of experience on gene expression.[14]

From a therapeutic perspective, both pharmacological and nonpharmacological modulations of gene expression have been shown to have potential efficacy in a variety of psychiatric disorders. Propionic acid, a major short-chain fatty acid produced by gastrointestinal bacteria such as Clostridia, can produce reversible behavioral and epigenetic changes closely resembling those found in autism when administered to rodents.[15] Cruciferous vegetables such as kale, cabbage, brussels sprouts, and broccoli sprouts contain chemical components, such as sulforaphane (SFN) and indole-3-carbinol (I3C), which have been revealed to be regulators of microRNAs (miRNAs) and inhibitors of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs).[16] Zimmerman et al. conducted a placebo-controlled, double-blind, randomized trial in which young men (aged 13–27) with moderate to severe autism received the phytochemical sulforaphane (n = 29) derived from broccoli sprout extracts or indistinguishable placebo (n = 15). The group receiving sulforaphane showed substantial declines (improvement of behavior). On CGI-I, a significantly greater number of participants receiving sulforaphane had improvement in social interaction, abnormal behavior, and verbal communication. Upon discontinuation of sulforaphane, total scores on all scales rose toward pretreatment levels.[17] These studies provide evidence that natural products which modify gene expression may have therapeutic efficacy in psychiatric disorders such as autism.

Several pharmacological and nonpharmacological epigenetic regulators have also been shown to exert antidepressant effects via inhibition of histone deacetylases.[18] Epigenetic regulation of type-2 metabotropic glutamate (mGluR2) receptors have recently been linked to antidepressant efficacy. Acetylcarnitine was found to have a rapid and enduring antidepressant effect on rats via promoting transcription of the mGlu2 receptor gene in the hippocampus and prefrontal cortex. L-acetylcarnitine promotes acetylation of histones and can induce mGlu2 receptor expression by increasing its acetylation.[19] Valproic acid, a drug approved for epilepsy and bipolar disorders, is a histone deacetylase inhibitor. Epigenetic drugs such as sodium butyrate show antidepressantlike effects in preclinical studies, and their efficacy is proposed to be mediated by facilitating demethylation and thereby enhancing specific expression of key genes involved in mood or memory. For example, an antidepressantlike effect of sodium butyrate has been demonstrated to be associated with an increase in BDNF gene expression.[20] These observations suggest that novel antidepressants which can favorably alter BDNF expression through epigenetic mechanisms should be further clinically assessed.

There is a growing interest in methylation disturbances and risk of depression. Nonpharmacologically, DNA methylation is accomplished through metabolism of methyl donors such as folate, vitamin B12, methionine, betaine (trimethylglycine), and choline. Diagnostically, several clinical labs are assessing specific DNA regions for use in psychiatric disorders. Methylenetetrahydrofolate reductase (MTHFR) genetic variation has been associated with vulnerability to certain psychiatric disorders, including depression. In one study, depression symptom severity varied by C677T genotype, with 677CC genotype showing the most severe symptom severity course over the 60 months of observation.[21] In a double-blind, randomized, placebo-controlled trial, patients with SSRI-resistant MDD received L-methylfolate 15 mg/d for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/d for 30 days,

or placebo for 60 days.[22] The effects of baseline levels of select biological and genetic markers individually and combined on treatment response to L-methylfolate versus placebo were evaluated; genetic markers related to disturbed methylation pathways predicted significantly ($p \leq .05$) greater reductions in depression scores with L-methylfolate versus placebo.[23]

Variation in the serotonin transporter gene (referred to as SERT or SLC6A4) has been suggested to impart differences in antidepressant treatment response. In one study, clinical response to treatment with escitalopram, an SSRI antidepressant, was assessed by changes of HAM-D scores after 6 weeks of treatment. Lower average methylation was seen across multiple CpG sites of the serotonin transporter, suggesting that DNA hypomethylation may increase serotonin transporter expression and thereby decrease serotonin availability and SSRI efficacy.[24]

In conclusion, an advance in our understanding of how changes in gene expression based upon environmental exposure influence brain development is a promising opportunity for preventive therapeutics in psychiatry.[25] The awareness that adverse child experiences can irreversibly modify the developing brain should give renewed urgency and attention to these effects, which can no longer be regarded as strictly psychological. In autism, preliminary evidence suggests that alterations in the gut microbiome can change the expression of gene pathways and that dietary interventions may favorably alter the disease trajectory. In PTSD, epigenetic changes of cortisol and BDNF regulatory sites offer exciting new opportunities to discover novel therapeutic agents that can modify the abnormal consolidation of memories related to trauma. Finally, in depression and schizophrenia, our understanding that key hypomethylated sites of gene expression offers us exciting new opportunities to target these disturbances with methyl-based dietary supplements.

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Prior to founding Genomind, Dr. Lombard served as the chief of Neurology at Bronx Lebanon Hospital where he led the Stroke Unit. He is also a former clinical assistant professor of neurology at New York Presbyterian Hospital, clinical instructor of Neurology and Medicine at Albert Einstein College of Medicine, and chief of Neurology at Westchester Square Medical Center and the Brain Behavior Center.

Dr. Lombard is a graduate of Nova Southeastern University College of Osteopathic Medicine. He combined his psychiatry and neurology residency training at Long Island Jewish Medical Center in New York.

Letters to the Editor

Marijuana and Apathy

I have been a physician for 61 years, during which time I directed many drug-abuse councils and worked with thousands of addicted/habituated young people as a psychiatrist and psychoanalyst and later as a practitioner of Chinese medicine.

I have been opposed to the "war on drugs" as misguided and doomed to fail to assess, define, and control the drug plague of the 20th and 21st centuries. I am in favor of medical marijuana under medical supervision. I am against police action and for education, however slow.

Nevertheless, I wish to register my experience with marijuana over these years as a substance extremely functionally, if subtly, destructive to people.

Subtly destructive, how?

Marijuana allows people to make extensive and sometimes unrealistic, even grandiose, plans for their lives, and robs them of the ability to realize these plans. They are left often with lives sometimes filled with excellent designs and without the will or energy to execute, to make decisions and follow through.

Among so many people, clients, friends, and acquaintances I have seen lives lived in fantasy and futility in many degrees of severity with endless energy-depleting maneuvers to hide their failure from others and themselves. Somewhere deep inside each loss is registered if not faced.

The reason is fear; fear of the emotions that would otherwise lead them to encounter struggle. Fear of their own anger and that of others was most often shared in the 1960s. A deep need to avoid confrontation and disapproval was most often cited.

This country, the richest in the world, is number 37 in the world in education and 27th in health care. We are not facing what is happening to our youth and our future. Creating generations of people who cannot cope with the endurance of pain for gain; generations of people who feel entitled to have what they should actually struggle for.

Marijuana has been a silent destroyer of the ability for 50 years, 3 generations, of our young people, to tolerate the inter- and intrapersonal frustration inherent to difficult long-term tasks. And now one of these generations is no longer young. Today not a few of these are introducing this drug to their children, actually and not infrequently.

During this period a narcoticized working class, middle and lower, has lost its earning ability and its capacity to have fought to keep it.

Western medical studies are long since quoted saying that marijuana is physiologically harmless. Of course people vary in their ability to detoxify it. According to Chinese medical studies, the story is different, a story that rests on a diagnostic methodology little understood and less accepted by a medical establishment largely and arrogantly ignorant of it.

Marijuana, according to Chinese herbal medicine, thousands of years old, is what is known as a "cold" herb, draining the essential energy called "yang" primarily from the liver, rendering it unable to perform its functions of physical and mental energy and containing it for when it is needed. The result is that when it is time to "move" on plans there is no coherent energy to do it.[1]

This, my thesis, is based on clinical experience with thousands of people over the past 50 years, experience that questions the value of "evidence-based" statistical biochemistry to correctly evaluate the mental and physical depredations of marijuana.

America, the human race, wake up: marijuana and the narcoticizing and simulating stable of substances, is devastating you as it soothes you into a permanent deep slumber and vulnerability.

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Notes

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Not All Homeopaths Object to Coffee

The July 2015 Letter from the Publisher comments on your concern that homeopaths advise patients that drinking coffee inactivates homeopathic medicines.

Actually, the observation that coffee antidotes homeopathic medicines is *not* universally accepted amongst homeopaths. In fact, there is no way that homeopathy could be as popular as it is in France, Italy, and throughout Europe (let alone South America) if coffee really did neutralize the healing potential of homeopathic medicines.

Further, many practicing homeopaths know that coffee is not the problem that it is presumed to be, because we know that many of our patients have occasionally or frequently drunk coffee without experiencing problems doing so.

In my experience as a homeopath since the 1970s, coffee may primarily be a problem in those patients who suffer from symptoms that coffee is known to cause. That is, because coffee is known to cause insomnia, irritable colon, and headaches, I generally recommend that people who have *these* ailments might benefit from avoiding coffee drinks. However, for the vast majority of people, I simply do not see coffee as a serious problem. In fact, I am not at all surprised to find that some research has found that people who drink 1 or 2 cups a day of coffee have reduced incidences of certain ailments.

I hope that these observations reduce the reasons that health and medical professionals may have to avoid the powerful nanomedicines used in homeopathy.

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Diet for a Healthy Brain

review by Katherine Duff

Grain Brain, by David Perlmutter, MD, with Kristen Loberg
Little, Brown and Company, Hachette Book Group; 237 Park Avenue, New York, New York 10017
© 2013; $27.00; hardcover; 323 pp.

Of all the diets being promoted in various media, one would be hard pressed to find one that focused exclusively on brain health. David Perlmutter, MD, has filled that void with his book *Grain Brain*.

One reason for the omission is the misconception that whether we develop Alzheimer's disease (AD) or other mental diseases is determined by our genes and may be inevitable. In other words, it is out of our control. Perlmutter offers another explanation: our genes determine how we process food, and they are still set for our much longer history of living and eating as hunter-gatherers than as farmers with our current agriculture-based diet. The focus of this book is on the role of diet and other decisions well within our control to maintain brain health.

The fact that the brain has no pain receptors may also explain why it has not been a consideration for diet and lifestyle choices. Inflammation that occurs in any other part of the body will alert us with pain and discomfort, but not in the brain. Evidence of inflammation, specifically elevated levels of cytokines, has been found in the brains of people suffering AD, multiple sclerosis, and other brain disorders. The search for sources of inflammation has taken Perlmutter to our diets, which include too many carbohydrates, too few healthful fats, and a growing problem with gluten sensitivity.

The exploration of carbohydrates' effects on the brain takes us to diabetes type 2, which is known to double one's risk of developing AD, and insulin resistance. These are not causes of brain disease, but, as Perlmutter notes, they share the same source: excess glucose in the blood. High levels of glucose circulating in the blood promote inflammation, which activates the production of free radicals, which leads to even more free radicals in the body, including the brain. In the case of insulin resistance, the high blood glucose levels can result in excess insulin in the blood. Insulin itself has an effect on other hormones that causes them to behave differently, affecting the body's ability to regain its metabolism. Insulin resistance also plays a role in the formation of plaques in the brain that displace normal cells. Food choices then must be those that are low on the glycemic index.

"Beyond calories, fat, protein, and micronutrients, we now understand that food is a powerful epigenetic modulator – meaning it can change our DNA for better or worse."

Gluten sensitivity has long been known to affect the small bowel; however, current research is implicating it in neurological disorders as well. The culprit is the antibody that forms against the gliadin in the gluten. This antibody switches on genes that cause cytokines to attack brain tissue. Compounding the problem is that the brain has certain proteins that appear very much like the gliadin protein. This leads to the antigliadin antibody combining with those proteins, causing production of even more cytokines.

Cognitive decline and brain disorders related to gluten sensitivity may be a concern for even more than the 30% of the population suspected of having gluten sensitivity. Perlmutter suggests that we may all be sensitive to gluten to varying degrees, and some physicians think it wise to test for gluten sensitivity for all patients in whom cognitive decline is present. The prevalence of gluten sensitivity may be increasing due to changes in food production that have resulted in a 40% increase in the amount of gluten in grains grown today compared with those grown just a few decades ago. And gluten is now added to many foods and other products, often under misleading names. The author has included lists to help identify various food sources and ingredient names.

The other branch of the brain diet calls for higher intake of "good" fats such as omega-3s and monounsaturated fats. Included in these is cholesterol. Rather than casting them as the scourge of modern diets, the author defines good fats as the preferred fuel of the human body, and cholesterol is one of those. It is needed for neurons and cell membranes and also acts as an antioxidant. Perlmutter cites several studies which have shown that high levels of cholesterol are linked with longevity in the elderly and are associated with higher scores on cognitive tests.

Part III of the book informs us how to implement the new diet and regimen using a 4-week plan. The first recommendation is a list of laboratory tests to establish a baseline, with the goal of repeating them at the end of 4 weeks. In order to increase energy and brain function, the author recommends fasting for 24 hours. This will cause the production of brain-derived neurotrophic factor, which protects neurons, assists in creating new neurons, and encourages synapse formation. Fasting

also enhances a pathway responsible for detoxification and reduction of inflammation.

After the fast, the regimen begins with the author's recommendations for brain health supplements and advice for formulating a diet high in proteins and good fats and very low in carbohydrates. There is advice for meal planning and recipes that demonstrate the new dietary balance. Weeks 2 and 3 focus on exercise and good sleep habits.

This brief overview of *Grain Brain* barely touches on all the information that the author uses to support adoption of the diet. But readers will undoubtedly have questions, since this is a diet very narrowly focused on brain health and there are no study outcomes yet. For example, the author eschews the need for supplemental antioxidants, and the diet has reduced consumption of fruits in favor of relying on the body's own antioxidant system. But we know that our modern atmosphere is stressing that system with continual assaults from polluted air and chemically contaminated water supplies. With more people tipping into conditions such as chronic fatigue syndrome and chemical sensitivity, is it really time to give up on our sources of exogenous antioxidants?

It is an eye-opening book, not just for the dietary advice but also because it will awaken the reader to the neglect of our most vital organ. While diets and lifestyle advice have generally focused on heart health, consideration of brain health has been nonexistent. A stunning example of this can be found in the prescribing of statins for high cholesterol. In targeting a supposed risk factor for heart disease, the side effect of memory dysfunction is barely regarded as consequential.

Alzheimer's disease is the most feared of all illnesses. Perlmutter has taken the all-important brain out of obscurity and given us reasons to consider its health in all our lifestyle choices.

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A Holistic Approach to Mood Disorders

review by Katherine Duff

Holistic Solutions for Anxiety & Depression in Therapy, by Peter Bongiorno
W. W. Norton & Company Inc.; 500 Fifth Avenue, New York, NY 10110
© 2015; hardcover; $37.50; 394 pp.

Holistic Solutions for Anxiety & Depression in Therapy by Peter Bongiorno could become a valuable resource for alternative and conventional physicians. Where conventional treatments for depression and anxiety rely on treating symptoms, usually with drugs, alternative treatment involves finding out the causes. In doing so, the investigation crosses several disciplines in conventional medicine including endocrinology, gastroenterology, neurology, and psychiatry. Patients dissatisfied with their drug treatments are increasingly turning to alternative methods to ease their mood disorders.

Author Peter Bongiorno is a naturopathic physician who works with patients who have mental health issues, where he utilizes conventional and alternative methods (CAM) of treatment. He works as part of a team that includes social workers, psychologists, psychiatrists, and therapists to provide insight into possible physical reasons for the depression and/or anxiety in the patient. These are complex conditions that usually involve multiple factors.

The statistics for anxiety and depression are eye opening. The World Health Organization has declared that depression is second only to heart disease as a burdensome disease that results in lost time and money. The US Centers for Disease Control and Prevention has found that 9.1% of the population suffers from depression, and of those, 4.1% have major depression. Anxiety is a feature in 58% of those with lifetime depression, and 48% of those with anxiety disorder also experience depression. But as the author notes, *depression* and *anxiety* are words that define symptoms, not causes. And rather than viewing anxiety and depression as separate conditions, the holistic physician sees them on a continuum. It is the task of the holistic physician to help find the causes and prescribe adjustments in diet, supplements, sleep, and nutrition.

The first order is to assess whether CAM treatments are advisable for a patient. With safety in mind, patients should be evaluated to determine whether they are in crisis. If so, pharmaceuticals from a prescribing physician may be necessary until the patient has calmed enough to address the causes. The CAM physician would need to be alert for ➤

this situation throughout treatment. There could also be contraindications for certain herbals and supplements. This of course begins with taking a good history, with special attention to mood issues and, as the author stresses, listening well.

"As the interest in CAM and natural medicine grows, a therapist who can speak knowledgably about integrative care will be of more value to the anxious or depressed client."

There are usually multiple causes for symptoms of depression and anxiety. The author addresses lifestyle factors that include sleep, diet, and exercise. Within the discussions are examples of stressors and some solutions. For example, sleep is a most important factor in mental health. For those who are night owls, cannot fall asleep, or have sleep apnea, those problems need to be addressed. In addition to describing how these problems can affect mood, the author proposes several solutions such as monitoring blood sugar before bed, keeping the room dark and cool, using a CPAP machine, and supplements.

The chapter about the internal factors that contribute to mood disorders contains the most fascinating discussions in the book. The possibilities are numerous, so the author begins with the blood and saliva tests that help to home in on the potential problems. An imbalance of blood sugar levels can have a direct effect on mood. Cholesterol is important, since it plays a role in the functioning of the serotonin receptors in the brain. Low cholesterol has been associated with anxiety and depression. High cholesterol is often treated with statin drugs, which can affect mood, especially in people who have already suffered depression. Thyroid tests could reveal an overactive thyroid, which results in anxiety and fast heart rate. A low thyroid would contribute to depressed mood and slowed thinking.

The digestive system is now known to play a large role in mental health. It is the gastrointestinal tract that is the main source of neurotransmitters. Bongiorno discusses the many conditions that can interrupt proper functioning, such as inflammation, stress, and poor nutrition.

The discussion of neurotransmitters may be particularly important since there has been considerable research into them for purposes of pharmaceutical development. Rebalancing neurotransmitters has been the goal in pharmaceutical therapy, but this book offers natural methods to rebalance them. Also in the book is advice for weaning a person off of pharmaceuticals. It would not be unusual for patients to already be taking such drugs when seeking holistic care, and there may come a time when they want to stop using them. The author stresses that this situation is not to be taken lightly. Incorrect withdrawal can cause permanent neurological damage. He advises a careful schedule and supplements to support the effort.

Whether correcting a deficiency or providing support, supplements and how they can affect mood are explained in a chapter that includes nutrient supplements, herbals, and homeopathy. That said, the author stresses getting one's nutrients from foods as much as possible.

The big picture of this book is that a coordinator is essential to discovering the causes of mood disorders. As Bongiorno notes, individuals are seeking help on their own through the Internet and supplement shelves. Some seek relief in street drugs and alcohol. If at all possible, the person would be much better off working with a trained physician and the team approach.

To paraphrase a comment from a neuroscientist whom I once read: there are many things that can go wrong in the human brain, but it is limited in its expression of the malfunction. And so it is with depression and anxiety. While many may exhibit the same symptoms, the causes may be very different. Bongiorno has taken the complex task of discovering the causes and parsed it into manageable sections. Further, for quick reference, he has synthesized the information into charts. The book is well written and well referenced, and includes resources. It could be a big step forward in alleviating the suffering of many. ◆

Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Applying Nanotechnology to Nutrition

One of the enduring challenges of medical therapies has been getting past the blood–brain barrier. Toxins need to be transported out of the brain and therapeutics shuttled in. Among the methods to traverse the blood–brain barrier has been small size. Because this issue of *Townsend Letter* is themed on the brain, I decided to research nanotechnology, manipulation of particles small enough to reach the brain and other body nooks and crannies. These particles hold great potential and unknown harms. Here are some examples of nanotechnology applications in food and health.

A Vision for Fewer Drug Side Effects

Researchers at Johns Hopkins's Wilmer Eye Institute have applied nanoparticle technology to solve an important clinical challenge. In the US, 1 in 10 corneal transplants ends up with rejection. Patients are required to take several eyedrops an hour, and most patients can't manage it. Not getting the medications right is the biggest reason for rejection. That's where the nanotechnology comes in. Nanoparticles enable a drug delivery system that releases medications over time, greatly simplifying the eyedrops needed after surgery. The same technology will be used to treat other diseases.

The lower net doses of corticosteroids required to treat eye diseases with nanoparticles are likely to benefit the corneal transplant recipients' overall health. One of the downsides of corticosteroid medicines is an increase in appetite and blood pressure. Even when used as eyedrops, corticosteroids create an uphill incline for patients' dieting efforts.

Phytonutrients: Vast New Potential with Nanotechnology

Curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), zeaxanthin, oleuropein, and allicin are among the many plant nutrients that benefit human health. While each of these phytonutrients is found in food sources, today each is just as readily available encapsulated as a dietary supplement.

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Now these plant nutrients are becoming available through a completely new delivery system using nanoparticles. Nutrients exert different effects throughout the body, and how it regulates and distributes nutrients still isn't known. Nutrients are part of the body's day-to-day metabolism. In this way they are different than medications, and more complicated to study and predict.

Nanoparticles are a new route of administration. For example there is p.o. (by mouth), IV (through the vein), and IM (through the muscle). Perhaps there should be a similar abbreviation for the nanoparticle drug delivery system. I'll suggest NT for nanotech routes.

To emphasize how much the route of administration can matter, I give the famous example of Dr. Linus Pauling's vitamin C research. Dr. Pauling cured patients by using vitamin C given both orally and intravenously, but others could not replicate his clinical results. As it turns out, the other researchers were using only oral vitamin C. Recently Dr. Mark Levine at the National Institutes of Health (NIH) explained that in vitamin C IV administration, the concentrations greatly exceed the highest blood levels of vitamin C that can be achieved from oral vitamin C alone. Not only that, at the higher concentrations, vitamin C acts as a prooxidant instead of an antioxidant. The route of administration of vitamin C made all the difference, but science still can't explain why it happens.

So, nanoparticles are a new route of administration of plant nutrients and they may hold great therapeutic potential. But, as with vitamin C, new routes will hold pharmacologic surprises too.

A Long 'Shadow' for Some Nanotechnology

Applying sunscreen got instantly easier with the use of nanotechnology. It's easier to apply sunscreens with nanoparticles of zinc oxide than conventional sunscreen, and they resist sweat and water.

Less unprotected skin seems like a very positive development, until one considers the unknown risks. I haven't been able to find satisfying answers to three potentially important questions on this topic:

1. Where is the zinc oxide going that it can elude sweat?
2. Metal oxides are regulated by the EPA as pesticides. Could the zinc oxide in my nano-sunscreen literally rub the microbiome the wrong way?
3. Since population studies inform us that our nation is vitamin D deficient, could long-acting sunscreen create "shade" for too long?

Nanoparticles in Food: Not Too Small to Matter

For my *Townsend Letter* columns, I research a topic and then write about the big picture that emerges from my research. I've tried to write about nanotechnology in food for five years. Whenever I do, the big picture stays blurry. Yet nanoparticles are definitely in our food supply and the business is said to be booming. Finally, while I was writing this column, it occurred to me that the blurry picture itself is a story.

1. Government websites don't inform us very well. Read about nanoparticles on the US site, and you'll be placated with the history of stained glass windows and medieval metallurgy rather than meaningful content about nanotech today.[1] There is no mention that medieval alchemists were considered as mad as hatters or that asbestos is a nanoparticle – one of few with safety studies.
2. Congress isn't empowering its regulators at the FDA. In fact, it seems harder now rather than easier for the FDA to develop its regulatory capacity around nanotechnology.
3. Transparent conversations are missing. Transparency continually incorporates new information. With nanotechnology, even though the technology is moving forward rapidly, Web discussions and public health research seem static. For example, other than by looking at the date, I can't tell if I'm reading a post or paper from 2008 or 2015.
4. Disclosure is not happening. There's no food labeling of nano-additives. One time they're in doughnuts, the next time they are in milk. But we can only learn of this through news reports or specialized testing, not by looking at the food. Based on the findings from lab animal research, a plan should be in place to inform the public.
5. Findings inconvenient to the nanotechnology industry are receiving short shrift. For example, fewer infections and increased shelf life are two benefits of nanoparticles in foods. However, the way that these benefits are achieved is by making the food unattractive to microbes. If the microbes in the refrigerator won't eat the food, our gut microbes won't eat it either. Without microbes, we can't digest our food well. And poorly digested food is a setup for food allergies. I haven't found research that considers these potential safety concerns arising from well-documented physiologic effects.

Nanotechnology holds great promise in some of its nutrition-related applications. Yet there's more to consider about the gut–brain connection than ever before. However, the absence of public dialogue around nano-foods is striking. Whatever the reason, public health appears to be seated at the back of the bus.

Notes

1. What is nanotechnology? [Web page]. National Nanotechnology Institute. http://www.nano.gov/nanotech-101/what/definition.

Ingrid Kohlstadt, MD, MPH, FACPM, FACN
Faculty Associate, Johns Hopkins Bloomberg School of Public Health
Executive Director, NutriBee National Nutrition Competition Inc.
Editor, *Advancing Medicine with Food and Nutrients* (CRC Press; 2013)

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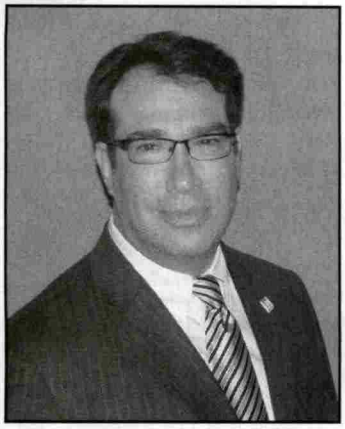
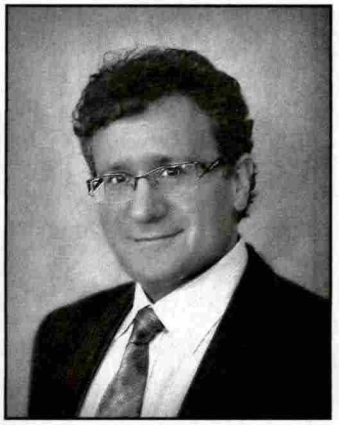


Anti-Aging Medicine

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



An Anti-Aging Approach to Alzheimer's Disease

Many of us question whether that forgotten fact is a "senior moment" – or something more foreboding. Dementia – a decline in thinking, memory, and learning skills, often accompanied by behavioral and social symptoms – is diagnosed in someone in the world every 4 seconds, introducing 7.7 million new cases annually. A progressive type of dementia that starts with mild memory loss, Alzheimer's disease (AD) affects the parts of the brain that control thought, memory and language. Today, AD is among the top 10 causes of death in the US, and its debilitating course of progression takes a toll on family and caregivers.

Presently, there is no known cure for AD. As such, it becomes imperative to know your risk factors so that you can prevent or delay its onset. This column reviews recent studies that suggest important considerations that may help you to be proactive in staving off AD.

US Centers for Disease Control & Prevention. Alzheimer's Disease [Web page]. http://www.cdc.gov/aging/aginginfo/alzheimers.htm. Accessed 2 July 2015.

Blood Type Linked to Cognitive Status

With aging, the amount of gray matter present in the brain declines – the extent of this reduction appears to correlate to blood type. Matteo De Marcoa and colleagues from the University of Sheffield (UK) utilized magnetic resonance imaging (MRI) to scan the brains of 189 healthy men and women, and calculated the volume of gray matter in the brain as a function of blood type. Data analysis revealed that the individuals with an O blood type had more gray matter in the posterior proportion of the cerebellum. Those with A, B, or AB blood types had smaller gray matter volumes in temporal and limbic regions of the brain, including the left hippocampus – the earliest part of the brain damaged by Alzheimer's disease. The study authors submit: "These findings identify the cerebellar tissue as a candidate for further studying ABO function, and support a general association between ABO blood type and variance in the development of the nervous system."

De Marcoa M, Venneri A. 'O' blood type is associated with larger grey-matter volumes in the cerebellum. *Brain Res Bull*. July 2015;116:1–6.

Low Fitness Raises Alzheimer's Risk

Mounting evidence suggests a preventive value for physical activity in the preservation of cognitive functions with age. Jenni Kulmala and colleagues from the University of Jyvaskyla (Finland) assessed data collected on 3559 men and women, average age 50 years at the study's start, enrolled in the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) study. The data revealed that among people in their 50s, those who self-rate their level of fitness as poor were 4 times more likely to develop dementia within 30 years than those who say they have a good level of fitness. Further, the team found that the link between poor self-assessment of physical fitness and dementia was strongest among people with chronic illnesses and those who did not carry the APOE4 gene (which is thought to associate with dementia). The study authors warn: "Perceived poor physical fitness reflects a combination of biological and lifestyle-related factors that can increase dementia risk."

Kulmala J, Solomon A, Kåreholt I, et al. Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study. *J Intern Med*. 2014 Jan 20.

Low Vitamin D Linked to Dementia

Older men and women with lower blood levels of Vitamin D may be at increased risk of dementia and Alzheimer's disease. David J. Llewellyn and colleagues from the University of Exeter Medical School (UK) reanalyzed data from the US Cardiovascular Health Study involving 1658 elderly adults. When the study began in 1993, none of the participants had dementia, heart disease, or stroke, and all gave blood samples for analysis. In 2008, a separate group of Cardiovascular Health Study of researchers retested the samples for circulating vitamin D levels. Whereas most people in the study did have sufficient vitamin D levels in their blood samples, defined as at least 50 nanomoles of the vitamin per liter of blood (nmol/L), about 30% of people had less than that: 419 people were deficient, with more than 25 nmol/L but less than 50, and 70 people were severely deficient, with less than 25 nmol/L. By 1999, 171 people in the study did develop dementia, including 102 cases of AD. The UK team ascertained that people who were severely deficient in vitamin D at the start of the study were more than twice as likely to develop dementia in the coming years as people with sufficient levels. The study authors write: "Our results confirm that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer disease."

Littlejohns TJ, Henley WE, Lang IA, et al. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*. 2014 Aug 6. pii: 10.1212/WNL.0000000000000755.

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Anti-Aging Medicine

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Chronic Sleep Disturbance May Trigger Alzheimer's Disease

People who experience chronic sleep disturbances may be at risk of developing dementia and AD at an earlier age. Domenico Praticò, professor of pharmacology and microbiology/immunology at Temple University's School of Medicine, and colleagues studied the effects of chronic sleep disturbances on a transgenic mouse model of Alzheimer's disease. The study began when the mice were approximately 6 months old – the equivalent of adult humans in their 40s. One group of mice was exposed to 12 hours of light and 12 hours of darkness, while a second group was subjected to 20 hours of light and just 4 hours of darkness, which greatly reduced their amount of sleep. At the end of the 8-week-long study period, the researchers found that the mice in the second group demonstrated significant impairment in their working and retention memory, as well as their learning ability. Examination of the animals' brains revealed no significant differences in amyloid plaque deposits between the two groups; however, the second group of mice had a significant increase in the amount of tau protein that had phosphorylated and formed tangles inside the brain's neuronal cells. "Because of the tau's abnormal phosphorylation, the sleep deprived mice had a huge disruption of this synaptic connection," said Praticò. "This disruption will eventually impair the brain's ability for learning, forming new memory and other cognitive functions, and contributes to Alzheimer's disease." The fact that the sleep-deprived mice developed the Alzheimer's brain pathology earlier than the mice that were not deprived suggests that chronic sleep disturbance acts as a trigger which accelerates pathological processes associated with dementia and AD. Praticò concluded: "We can conclude from this study that chronic sleep disturbance is an environmental risk factor for Alzheimer's disease."

Di Meco A, Joshi YB, Praticò D. Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. *Neurobiol Aging*. Feb 15, 2014.

Cholesterol May Predict Alzheimer's Marker

A person's patterns of LDL cholesterol and HDL cholesterol may influence the levels of amyloid-beta protein present in the brain, which typifies AD. Bruce Reed and colleagues from the University of California/Davis (US) studied data collected on 74 men and women, average age 70 years, who had normal to mildly impaired cognitive function. The team studied the participants' cholesterol levels, as well as measured brain deposits of amyloid-beta protein. They found that on average, those who had higher levels of the low-density lipoprotein (LDL, "bad") cholesterol and lower levels of high-density lipoprotein (HDL, "good") cholesterol had higher levels of amyloid in the brain. Observing that "Elevated cerebral [beta-amyloid] level was associated with cholesterol fractions in a pattern analogous to that found in coronary artery disease," the study authors posit "an important role for cholesterol in [-amyloid-beta] processing."

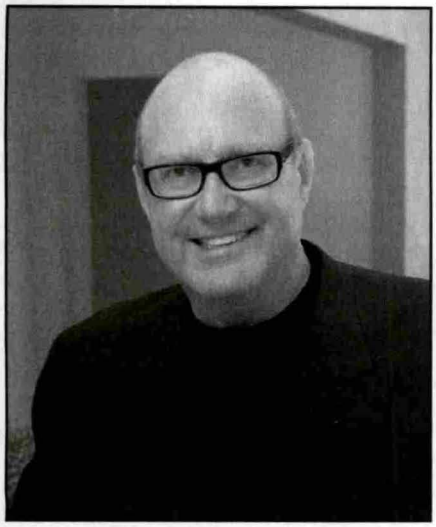
Reed B, Villeneuve S, Mack W, DeCarli C, Chui HC, Jagust W. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurology*. Dec. 30, 2013.

Lifestyle Factors Affect Risk

In many aspects, the anti-aging lifestyle is anti-Alzheimer's. Deborah Barnes and colleagues from the University of California, San Francisco (US), have identified seven key risk factors for which there is consistent evidence of an association with AD; namely, diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment. The researchers estimate that by reducing the relative risk from each of these risk factors by 10%, it will be possible to reduce the prevalence of Alzheimer's in 2050 by 8.5%, preventing 9 million cases. The study authors write: "Around a third of Alzheimer's diseases cases worldwide might be attributable to potentially modifiable risk factors. Alzheimer's disease incidence might be reduced through improved access to education and use of effective methods targeted at reducing the prevalence of vascular risk factors (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes) and depression."

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. August 2014;13(8):788–794.

To stay updated on the latest breakthroughs in natural approaches that may help you to reduce your risks of Alzheimer's, visit the World Health Network (www.worldhealth.net), the official educational website of the A4M and your one-stop resource for authoritative anti-aging information. Be sure to sign up for the free Longevity Magazine e-journal, your weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity. ◆



Monthly Miracles

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

Anxiety, Depression, and Psychosis

I have always been interested in mental illness, which I have studied since my postdoctoral years at the Palo Alto VAH and the Stanford Research Ward. This was home to *One Flew Over the Cuckoo's Nest*. The universal take on mental illness is that it is a multifactorial problem, and I observed that the standard pharmacological treatment was extremely heavy handed and frightening. I occasionally was the person who tackled escapee psychotic patients on the hospital grounds and restrained them until the nurse arrived with intramuscular injections of Thorazine, a chemical restraint. It still leaves an indelible impression. Bless us all to evolve to more humane and reasonable treatments for mental ailments.

Remembering the woodcuts from the "Bedlam" asylum in 17th-century England with the wild-eyed inmates pressing their faces against the bars reminds us that adrenaline, sympathetic dominance, is an old problem. Dopamine antagonists still rule in psychotic therapy and emptied the mental hospitals in the 1950s and 1960s. I worked one summer at the Stockton (California) State Mental Hospital, which once housed 15,000 patients; by the time I was there, in 1969, the patient population was only 1500, thanks to phenothiazines. Modern antipsychotics, antidepressants, and anxiolytic drugs are more user friendly but are still in the dark ages of medical practice.

Multiple Causations for Mental Illness

Causes include unrelenting stress, PTSD, sexual and physical abuse, Lyme disease, chronic viral illness, parasitic diseases, inherited genetic weakness such as MTHFR, homeopathic miasms, environmental illness, heavy metal toxicity, root canals with infected teeth, bad diet, and nutritional deficiencies. Many other factors such as candida, mold, unfortunate maternal stress during the third trimester of pregnancy giving transgenerational adrenal weakness, thyroid insufficiency in the face of normal blood tests, menstrual disorders, and hormone imbalance also contribute to mental illness.

So Many Helpers, but Remember Progesterone

There is a pretty awesome repertoire of healing modalities for mental illness. Thyroid replacement with either porcine or bioidentical T3 and T4 has been reviewed in several previous issues of the *Townsend Letter*. Puffy, cold, hair-losing women who are constipated, fatigued, and depressed need a trial on thyroid. Those patients lacking energy with sleep issues need adrenal support. Use cortisol à la Jefferies 5 mg b.i.d. or q.i.d. and/or adrenal shots of cortisol, DHEA, and pregnenolone with methyl B12 and folic acid (see my previous columns). Amino acid precursor therapy for neurotransmitter rebuilding with 5-HTP, tyrosine, and cysteine is awesome although a little expensive and time consuming with a 4 times per day treatment regimen. Most magnificently, topical progesterone, an adrenal hormone precursor, at 50 mg per pump rubbed into the forearms blocks adrenaline and increases GABA in 3 to 10 minutes. Anxious, panicky, and psychotic patients often relax, and application can be repeated every 5 to 15 minutes or hourly until the adrenaline response diminishes. Progesterone is not feminizing and can be used for men and children. (I have particularly loved the websites for transgender folks who say that progesterone is absolutely not good for developing breasts in males.) I have given it to a 3-week-old girl who was in agony from colic with her back arched and screaming. After a pea-sized dot of progesterone was rubbed into her forearm, she was calm and asleep in about 3 minutes. Patients who are going out of their skin with fear, hopelessness, difficulty concentrating, and surety that they will never recover from their illness are immediately soothed by progesterone. Thanks, Dr. Michael Platt.

A Nice Case

A 39-year-old jeweler with a history of scabies and chronic skin conditions and who had been helped with homeopathic sulfur 1M had indulged in strong cannabis and/or psychedelic drugs that rendered him paranoid, insomniac, and anorexic for about 10 days. He was rambling with paranoid content ("My friends are trying to kill me at my local bar, they are poisoning me"), dilated pupils, and hair standing on end, which he described as a fashion statement. He was accompanied by his mother who is a craniosacral therapist and very supportive of her son. We began his therapy with our antipsychotic intravenous therapy of L-tryptophan, L-taurine, magnesium, calcium, vitamin C 25 grams, B complex, zinc sulfate, potassium chloride, FreAmine 8.5% 25 ml, aqueous hydrocortisone 0.2 mg/ml 10 ml, L-glutathione 200 mg/ml 2.5 ml. He received this for 2 days in the first week and then one more time until he stopped testing well for this IV. We gave our usual intramuscular injection of adrenal complex, as above with methyl B12, and folic acid every other day for a week and then twice weekly. He was given high-dose vitamin C, B2, and inositol hexanicotinate. Topical progesterone cream was very helpful in the first 15 minutes. He resumed eating and sleeping, and his paranoia was reduced markedly in the first week. Lachesis 200 C homeopathically was most helpful for symptoms of nervousness; excitability; great loquacity; rambling; frequently jumping from one subject to another; delusions of thinking himself under superhuman control; feeling pursued, hated, and despised; fears going to sleep; having no desire to mix with the world; insane jealousy and suspicion; and feeling full of poison.[1]

He is now back to work, sleeping and eating normally, and not exhibiting paranoid symptomatology.

Notes

1. Murphy R. *Homeopathic Remedy Guide*. H.A.N.A. Press; 2000.

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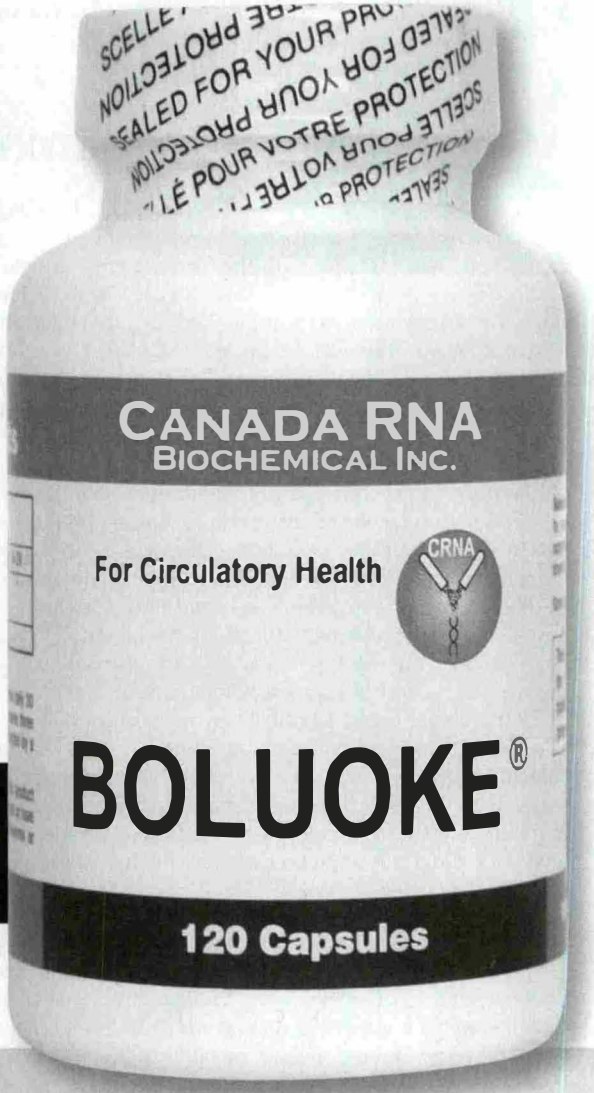
- ✔ Modifies CA-cell adhesion: ↓P-Selectin, ↓E-Selectin
- ✔ Decreases microbial resistance: breaks down biofilm
- ✔ No significant effect on INR or PTT



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SEPTEMBER 25-26: NEW FRONTIERS IN GI MEDICINE in Dallas, Texas. CONTACT: 561-997-0112; www.a4m.com/2015-09-dallas-gi-symposium.html

SEPTEMBER 25-27: METAGENICS EDUCATIONAL PROGRAMS present 2015 LIFESTYLE MEDICINE ON HEALTHY AGING in Phoenix, Arizona. CONTACT: 800-692-9400 (US) or 800-268-6200 (Canada); www.metagenics.com/2015summit

SEPTEMBER 30-OCTOBER 3: INTERNATIONAL PLANT-BASED NUTRITION HEALTHCARE CONFERENCE in Anaheim, California. CONTACT: 203-594-1632; pbnhc.com

OCTOBER 1-4: 13th ANNUAL RESTORATIVE MEDICINE CONFERENCE in Blaine, Washington. CONTACT: restorativemedicine.org/conference/2015/

OCTOBER 2-3: INTEGRATIVE THERAPIES INSTITUTE presents IMMUNE & AUTOIMMUNITY in Philadelphia, Pennsylvania. CONTACT: www.itiphilly.com

OCTOBER 2-4: 17th ANNUAL CANADIAN ENERGY PSYCHOLOGY CONFERENCE in Ft. Lauderdale, Florida. Pre- & Post-conference workshops on trauma, heart-assisted therapy, Callahan techniques & more. CONTACT: www.epccanada.ca/

OCTOBER 2-4: HORMONE REPLACEMENT THERAPY SEMINAR (Session 2) with Dr. Neal Rouzier in Chicago, Illinois. CONTACT: www.ducerecorp.com/Seminars.aspx

OCTOBER 3-4: WANP ANNUAL NATUROPATHIC CONFERENCE – Naturopathic Perspectives on Cardiometabolic Health in Lynnwood, Washington (near Seattle). CONTACT: www.wanp.org

OCTOBER 4: WOMEN'S HEALTH CONFERENCE in Phoenix, Arizona. Urinary & sexual health and hormones. CONTACT: www.drmarchese.com/womenshealthconference.html

OCTOBER 9-11: 15th INTERNATIONAL CONFERENCE ON AYURVEDA & AUTOIMMUNE DISORDERS in San Jose, California. CONTACT: aapna.org/conferences/15th-conference-october-9-11-2015-san-jose-ca-usa

OCTOBER 10: BIOTICS RESEARCH presents UNDERSTANDING, EVALUATING, AND ADDRESSING AUTOIMMUNE DISORDERS in Irving, Texas. CONTACT: https://dl.dropboxusercontent.com/u/49027318/Kleber_Dallas%20Flyer.pdf

OCTOBER 14-17: MINDFUL PRACTICE ADVANCED WORKSHOP: Enhancing Quality of Care, Quality of Caring, and Resilience in Batavia, New York. For healthcare practitioners. CONTACT: www.urmc.rochester.edu/family-medicine/mindful-practice/presentations-workshops.aspx

OCTOBER 15-18: ILADS 2015 CONFERENCE in Fort Lauderdale, Florida. CONTACT: www.ilads.org/lyme_programs/ilads-conferences.php

OCTOBER 17: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Boston, Massachusetts. Also, **DECEMBER 5** in Los Angeles, California. CONTACT: www.greatplainslaboratory.com/home/eng/OATworkshop.asp

OCTOBER 21-24: 10th ANNUAL CARDIOMETABOLIC HEALTH CONGRESS in Boston, Massachusetts. CONTACT: www.cardiometabolichealth.org/register.asp ➤

Douglas Laboratories Launches New Line of Vision Health Supplements

Healthy aging is a hot topic today, particularly as the Baby Boomer generation enters its 50s. While attention is frequently given to strong bones and maintaining cognitive health as people age, little consideration is given to vision health. Now, three new nutritional products from Douglas Laboratories are available to support healthy eye function during the aging process, all utilizing the latest research.* This suite of ocular formulas includes Ultra Preventive Vision, Macu-Support, and Eye Moisture Support.

"Science continues to emerge regarding the role nutrition plays in eye health," said Dr. Stuart Richer, OD, PhD, FAAO, codeveloper of the new suite of vision health products for Douglas Laboratories. "We've utilized the latest research to create three new nutritional supplements to support healthy eye function."*

Ultra Preventive Vision is a comprehensive multivitamin/mineral formula with phytonutrients and carotenoids specially designed to help support a healthy macula, retina, and visual performance for all ages that are affected by excess blue-light exposure and free radical damage.*

Macu-Support supplies a well-balanced spectrum of key antioxidants that are important in maintaining normal retina and macula function in the eyes. As we age, the ability of the macula to function properly can decline. The nutrients found in Macu-Support have been studied for their ability to help maintain and support macular function and health.*

Eye Moisture Support is a unique dietary supplement featuring QÜELL Fish Oil, organic borage seed oil, and astaxanthin, among other nutrients, for healthy production of tears and moisture in the eyes.*

"At Douglas Labs, we strive to offer a comprehensive line of nutritional supplements for healthy aging," said Andrew Halpner, PhD, vice president, Product Development and Technical Services at Douglas Laboratories. "The ocular formulas that were codeveloped with Dr. Richer are a great addition to our existing line of products to support vision health as we age."*

For more information on Ultra Preventive Vision, Macu-Support, and Eye Moisture Support, please visit www.douglaslabs.com.

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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Calendar

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OCTOBER 23-24: CONCORDIA: The Legacy Continuum 2015-BioEnergetic Functional Medicine in Santa Barbara, California. CONTACT: physicaenergetics.com/dv/pages/Annual-Conferences.html

OCTOBER 24-29: 16TH ANNUAL SCIENCE AND CLINICAL APPLICATION OF INTEGRATIVE HOLISTIC MEDICINE in San Diego, California. CONTACT: www.scripps.org/events/people-planet-purpose-global-practitioners-united-in-health-healing-october-25-2015

OCTOBER 27 - NOVEMBER 2: 42nd BIOLOGICAL MEDICINE TOUR TO GERMANY & BADEN-BADEN MEDICINE WEEK – "Clinical Applications in Biological Medicine." Includes"Medicine Week" Congress, exclusive OIRF English language lectures, and instrumentation, clinic and pharmacy presentations. **CONTACT**: Occidental Institute at 800-663-8342 or 250-490-3318; fax 250-490-3348; support@oirf.com; www.oirf.com

OCTOBER 28-NOVEMBER 1: ICIM CONFERENCE – ENERGY & MEDICINE: PARADOX & CONTROVERSY in Chicago, Illinois. CONTACT: www.IntegrativeMedicineConference.com

NOVEMBER 6-8: ENERGY ADVANCED PRACTICE MODULE – ILLUMINATING THE ENERGY SPECTRUM in Dallas, Texas. Live Streaming Available. CONTACT: www.functionalmedicine.org/Energy

NOVEMBER 6-8: GI ADVANCED PRACTICE MODULE – RESTORING GASTROINTESTINAL EQUILIBRIUM in Dallas, Texas CONTACT: www.functionalmedicine.org/GI

NOVEMBER 7-8: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION 2015 FALL CONTINUING MEDICAL EDUCATION CONFERENCE in Scottsdale, Arizona. CONTACT: www.aznma.org

NOVEMBER 7-8: NUTRITIONAL INTERVENTIONS YOU WILL USE EVERYDAY in Orlando, Florida. CONTACT: 800-231-5777; https://www.facebook.com/BioticsResearch

NOVEMBER 11-13: 56th AMERICAN COLLEGE OF NUTRITION ANNUAL CONFERENCE in Orlando, Florida. CONTACT: americancollegeofnutrition.org/conference

NOVEMBER 12-14: SOCIETY FOR ACUPUNCTURE RESEARCH 2015 CONFERENCE in Boston, Massachusetts. CONTACT: www.acupunctureresearch.org/events

NOVEMBER 12-15: 20th WORLD CONGRESS OF AESTHETIC MEDICINE in Miami, Florida. CONTACT: www.aaamed.org/20wcam/

NOVEMBER 12-15: AMERICAN COLLEGE FOR ADVANCEMENT IN MEDICINE (ACAM) CONFERENCE in Las Vegas, Nevada. CONTACT: https://acam.site-ym.com/page/2015Welcome/?

NOVEMBER 12-15: AMERICAN FUNCTIONAL MEDICINE ASSOCIATION ANNUAL CONFERENCE in Atlanta, Georgia. CONTACT: 1-855-500-2362; www.afmassociation.com

NOVEMBER 13-14: CASI – Clinical and Scientific Insights in Functional & Lifestyle Medicine in New York, New York. CONTACT: Jenny, 860-752-7441; www.casitalks.com

NOVEMBER 13-15: IGNITE CONFERENCE 2015 – The Business of Better Medicine in San Diego, California. CONTACT: eeignite.com/coming-soon-the-business-of-better-medicine

NOVEMBER 14: ACHIEVE OPTIMAL WELLNESS WITH DETOXIFICATION in Bethesda, Maryland. CONTACT: 800-231-5777; https://www.facebook.com/BioticsResearch.

NOVEMBER 14-16: 12th INTERNATIONAL CONFERENCE OF THE SOCIETY FOR INTEGRATIVE ONCOLOGY in Boston, Massachusetts. CONTACT: www.integrativeonc.org/annual-international-conference

NOVEMBER 19-21: BIO-IDENTICAL HORMONE REPLACEMENT THERAPY SYMPOSIUM in Vancouver, British Columbia, Canada. CONTACT: 561-893-8626; www.A4M.com

NOVEMBER 19-22: 5th ANNUAL PRO-AGING EUROPE CONFERENCE with Dr. Thierry Hertoghe in Brussels, Belgium. CONTACT: https://www.weezevent.com/pro-aging-europe-2015

DECEMBER 10-13: 23rd ANNUAL WORLD CONGRESS ON ANTI-AGING MEDICINE in Las Vegas, Nevada. CONTACT: 561-893-8626; www.a4m.com/anti-aging-conference-lasvegas-2015-dec.html

JANUARY 29-31, 2016: WORLD CONGRESS ON NATURAL MEDICINES in Tampa, Florida. CONTACT: www.smoch.org/world_congress_tampa.php

JANUARY 29-31: 2016 PHYSICIAN'S ROUND TABLE CONFERENCE in Tampa, Florida. CONTACT: 352-687-2399; www.suevogan.net

FEBRUARY 4-6: CARDIOMETABOLIC ADVANCED PRACTICE MODULE - Prevention of Chronic Metabolic and Cardiovascular Disorders in Atlanta, Georgia. CONTACT: www.functionalmedicine.org/Cardiometabolic

FEBRUARY 7-9: IMMUNE ADVANCED PRACTICE MODULE - The Many Faces of Immune Dysregulation and Chronic Inflammation in Atlanta, Georgia CONTACT: www.functionalmedicine.org/Immune

FEBRUARY 19-21: LDN 2016 CONFERENCE in Orlando, Florida. CONTACT: www.ldn2016.com/townsend/

MARCH 4-6: ENVIRONMENTAL HEALTH SYMPOSIUM ANNUAL CONFERENCE in San Diego, California. CONTACT: www.EnvironmentalHealthSymposium.com

MARCH 14-18: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE – 5 day foundational course in Phoenix, Arizona CONTACT: www.functionalmedicine.org/AFMCP

MAY 12-14: THE INSTITUTE FOR FUNCTIONAL MEDICINE'S 2016 ANNUAL INTERNATIONAL CONFERENCE – Creating Balance *Between* Motion and Rest in San Diego, California. CONTACT: www.functionalmedicine.org/AIC

MAY 17-20: INTERNATIONAL CONGRESS FOR INTEGRATIVE MEDICINE & HEALTH - Bridging Research, Clinical Care, Education, and Policy in Las Vegas, Nevada. With IHPC, ACCAHC, AIHM and ISCMR. CONTACT: www.icimh.org/

JULY 15-17: HORMONE ADVANCED PRACTICE MODULE – RE-ESTABLISHING HORMONAL BALANCE in National Harbor, Maryland (DC) CONTACT: www.functionalmedicine.org/Hormone

JULY 15-17: ENERGY REGULATION ADVANCED PRACTICE MODULE – Illuminating the Energy Spectrum in National Harbor, Maryland (DC) CONTACT: www.functionalmedicine.org/Energy

SEPTEMBER 19-23: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE - 5 day foundational course in Baltimore, Maryland. CONTACT: www.functionalmedicine.org/AFMCP

OCTOBER 28-30: DETOX ADVANCED PRACTICE MODULE – Biotransformation and Toxicity in Chicago, Illinois. Live Streaming Available. CONTACT: www.functionalmedicine.org/Detox

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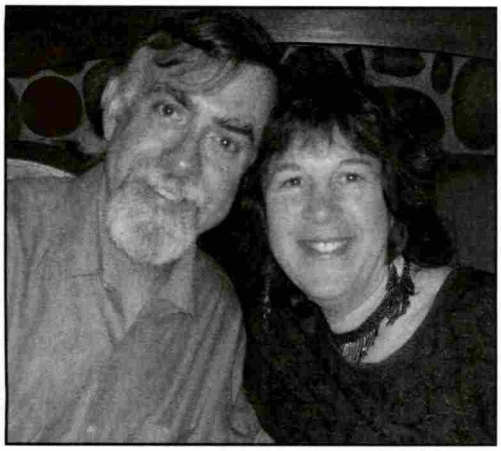

Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, DHANP, LCSW, and Robert Ullman, ND

www.healthyhomeopathy.com

Homeopathy: Affordable Medicine

Out-Of-Sight Pharmaceutical Drug Costs

Exorbitant, skyrocketing, out-of-control ... these words are commonly used to describe the cost of health-care services and drugs in the US as compared with the rest of the world. It is no surprise that a growing number of our compatriots are taking medical and dental vacations to such affordable and desirable destinations as Thailand, India, Mexico, Canada, Germany, Costa Rica, Israel, Singapore, the UK, Panama, Spain, and, in our case, Chile. We have gotten colonoscopies at a first-rate Chilean hospital for $240 (compared with over $2000 in the US), laboratory testing (under $200 at a local medical lab for what would cost $1000+ here), and dental care (our Argentine dentist there charges less than 1/3 for comparable care here and is an endodontist with nearly 30 years of experience). A 30-minute IV infusion of Zometa (a relative of Fosamax that has been shown as a possible preventive treatment for estrogen-positive breast cancer survivors) cost us $3500 here compared with $500 down there!

In fact, health-care fees in the US are so scary that smart Canadians dare not set foot across our border unless they have some type of traveler's health-care insurance. A little jaunt in our country, however brief, could bankrupt them if they happened to suffer a health mishap, even a relatively minor one. A recent article in AARP bulletin, "Prices Spike for Some Generics," by Peter Jaret (July–August 2015), boggled our minds. Would you believe that the annual cost of 500 capsules of doxycycline hyclate, a commonly prescribed antibiotic, soared from $20 in the fall of 2013 to an unbelievable $1849 in April of the following year? There were many other shocking examples of sky-high pharmaceutical inflation. Pravastatin sodium 10 mg (one of those widely touted, and lately highly controversial, statin drugs recommended to lower cholesterol) nearly doubled in price last year from $849 to $1700. And the article discussed only generic drugs, which cost the patient far less than nongenerics. Scary enough for those of us included in the health-care safety net of Medicare or Obamacare, these soaring prices are enough to bankrupt someone on a fixed income.

How, the author of the AARP article queries, is it possible for generic drugs, which account for about 80% of all prescriptions, to have spiked so dramatically in price? Basically because drug manufacturers, especially when there are fewer of them, can charge what they please. And pharmaceutical company mergers make for less competition in the marketplace. The result: of the 280 generics in the marketplace in this country, 73% decreased in cost in 2013 and 27% "went up, in some cases into the stratosphere."

Homeopathy Rather Than the ER for First Aid and Acute Illnesses

Before we get into a discussion about comparative costs of homeopathy and conventional care, let us tell you first and foremost about the *effectiveness* of homeopathy for these conditions. *Arnica* alone is of tremendous benefit in many, if not most, non-life-threatening first aid situations. There are many medical situations in which homeopathy alone can take care of the problem. This may be either through self-care or treatment with a professional homeopath.

Let's talk first about first-aid conditions such as sprains and strains, cuts, scrapes, and puncture wounds. An eye-opening NIH (National Institutes of Health)-funded study investigating the escalated cost of medical bills examined over 8300 emergency room bills (February 2013). It found that the average ER bill was $1233 (40% more than the average American was paying for a month's rent) and that the cost of treating a sprained ankle ranged from $4 to $24,000!

Nonemergency first-aid conditions can, in our experience, be treated highly effectively with homeopathy,

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often without the assistance of a physician or homeopath. Our tried-and-true book *Homeopathic Self-Care: The Quick and Easy Guide for the Whole Family* has sold over 30,000 copies and provides clear, simple, straightforward guidelines for self-treatment. Armed with this or another self-care book and a homeopathic medicine kit, such as our companion *Homeopathic Self-Care Home Medicine Kit* (50 remedies in 30C potency), families can save a small fortune.

If you know only three or four remedies and their indications (let's say *Arnica*, *Bryonia*, *Rhus toxicodendron*, and *Ruta*), you can very likely save a trip to the doctor. The cost of the book and kit, for example, is under $120. The remedies never expire – they will last a lifetime unless they run out from frequent use. It would not even occur to us to seek conventional care for a strain or sprain. Nor have we ever had a patient, in our 30-plus years in practice, who did not find relief with homeopathy, within minutes or hours, from a sprain or strain. Of course, we recommend icing, elevating the sprained area, and avoiding putting pressure on it temporarily. But an ER or even urgent-care visit wouldn't even occur to us. Nor to patients familiar with homeopathy. For the average ER bill of $1233 in 2013 for an ankle sprain (surely higher in 2015), you could pay for the entire first year of homeopathic constitutional care for a chronic problem, including all the remedies!

We remember, years ago, a mom who called us about her son who suffered a laceration of his cornea after running into a tree branch. She had raced him to the ER prior to bringing him to our office. We gave a high-potency dose of *Arnica* (1M). The ER doc told her he might need surgery the following morning if the corneal abrasion didn't improve. She called us, much relieved, to report that his eye had healed remarkably in 12 hours and that no surgery would be needed. That was no surprise to us. Simply put, the body has a remarkable ability to heal itself when given even a nudge in the direction of healing, which is what happens with homeopathy. So simple, often, that it is hard to attribute the rapid response to those little white pellets!

The National Hospital Ambulatory Medical Care Survey estimated that one-third to one-half of all ER visits are for non-urgent care. The top three conditions resulting in ER visits in 2007, for example, were for superficial injuries and contusions, sprains and strains, and upper respiratory infections. (Debt.org: *Emergency Rooms vs. Urgent Care: Differences in Services and Costs,* by Bill Fay) Granted, many of these visits resulted from the fact that federal law mandates urgent care to all patients, regardless of their ability to pay. Consequently, patients without health insurance or adequate funds to pay out-of-pocket costs typically use emergency rooms as their main health-care providers. It is estimated that over $18 billion could be saved annually if these individuals with non-urgent problems were to seek treatment outside emergency-care facilities. Back in 2011, the average cost of an ER visit for someone with private health care insurance was $933. Based on the average number of claims submitted in 2010 to the Medica Choice Network, including over 4000 medical offices across four Midwestern states, these are average ER costs:

- allergies: $345 (urgent care centers: $97)
- acute bronchitis: $595 ($127)
- earache: $400 ($110)
- sore throat: $525 ($94)
- sinusitis: $617 ($112)
- upper respiratory infection: $486 ($111)
- urinary tract infection: $665 ($110)

In our self-care book, we include nearly 70 first-aid and acute conditions that are highly amenable to homeopathic self care. We provide guidelines about when emergency care is indeed needed, such as for severe burns. That said, distraught parents called us over the weekend one time, alarmed that their 5-year-old daughter had inadvertently sat on top of a woodstove. We recommended that she take *Cantharis* immediately, and she was much improved by the following day and needed no conventional care. We are, of course, not talking about appendicitis, which can be life threatening and requires immediate care. Bob, for instance, suffered from peritonitis, as a complication of appendicitis, resulting in a 6-day hospitalization.

Homeopathic self-care can yield brilliant results for colds, flu, earache, allergies, acute bronchitis, urinary tract infections – all conditions included in the list above. If the response is not clear within 12 to 24 hours, or if symptoms worsen, *then* urgent or outpatient clinic care can be sought. Again, homeopathic self-care books provide indications of what is serious and what is not. A number of years ago, the afternoon before his scheduled 50th birthday party, Bob started feeling exhausted and developed a cough. By bedtime he was shivering and was breathing rapidly. Early the next morning he coughed up blood in the bathroom sink. We drove immediately to the ER, he was diagnosed with double bacterial pneumonia, and he was hospitalized for several days. That condition did, without question, necessitate hospitalization. Similarly, Judyth had a long-distance patient who moved from Seattle to the Midwest. He called due to a bad cough of several weeks' duration. She told him to go the ER immediately, upon which he was first sent home then, the next day, diagnosed with pneumonia. By that time, an antibiotic was what he needed. However, most of the time it will be bronchitis, which will improve within 1 to 3 days with homeopathy. A bladder infection, though frequently highly painful, typically responds to homeopathic care within 15 to 30 minutes. The nearly 70 conditions that we include in our self-care book generally remit very quickly with the right

homeopathic remedy. And, if self-treatment isn't working, you can always call your homeopath for some expert guidance – at a fraction of what you would pay for an ER visit, not to mention the prescribed pharmaceuticals.

Constitutional Homeopathic Care: Bargain Medicine

We have a long-range perspective on keeping people healthy, having worked with some of our patients for 30 years. In fact, we spoke with one today. She is now 78 and homeopathy has kept her much healthier than could have been expected for 30 years. We are talking about such significant problems as acute psychosis, incontinence, musculoskeletal and gait problems, and, most recently, heart arrhythmias. She has lived on a shoestring the entire time, and had few medical expenses prior to her Medicare coverage. Even now, she finds that she enjoys better health without the statins and beta blockers that her physician recommended. It is, of course, her choice, to which her MD is resigned. Her family is well aware of her benefit from and loyalty to homeopathy.

Constitutional homeopathic care means treating the whole person for any and all health problems – physical, mental, and emotional – with a single homeopathic medicine. The annual cost, including an initial 90-minute visit and a maximum of 8 return visits (often less), adds up to $1600 maximum the first year of care and, on an average, under $1000/year in subsequent years. Add the cost of the homeopathic remedies (maximum $200/year but often far less) and compare this with the cost of conventional medical care, much less ER and urgent-care visits.

We repeat: homeopathy treats the whole person. Although nutritional supplements can be very helpful, the number of those recommended to homeopathic patients is far less than with CAM (complementary and alternative medicine) care. And a fraction of what a child on the autism spectrum will be taking if being treated by a Defeat Autism Now! (DAN!) protocol doctor. Not to mention that homeopathic treatment, in our experience, often replaces expensive psychiatric medications. Whether you choose to treat yourself or your family for first aid and acute problems with a homeopathic kit, or to seek professional care with an experienced homeopath, you will save a bundle and mostly likely end up much healthier in the process!

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy, in practice for over 30 years. Check out our redesigned, user-friendly website www.healthyhomeopathy.com, with lots of free articles, mini-books, and information about our 9 books and our practice. We live on Whidbey Island, Washington, and in Pucón, Chile, and practice at the Northwest Center for Homeopathic Medicine in Edmonds, Washington. We treat patients in person and by phone or videoconference. Call us at 425-774-5599, or e-mail drreichenberg@gmail.com or drbobullman@gmail.com.

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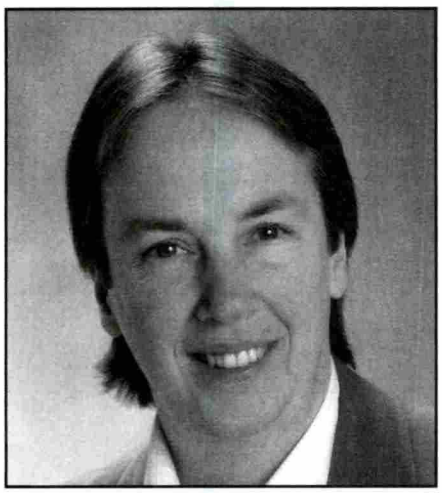

Women's Health Update

by Tori Hudson, ND and
womanstime@aol.com

Omega-3s and Mental Health

Omega-3 Marine Oils and Depression

When it comes to the biological basis for mental health disorders, the presumption is that there is an abnormality of neurotransmitters – whether it be an excess, deficiency, or abnormal interactions with receptors and transporters. While the focus of current pharmacological therapy is the neurotransmitter and its proteins, the impressive role of lipids, particularly long-chain polyunsaturated fatty acids (LC-PUFAs), cannot be overstated. The weight of the brain is roughly 60% lipid, the richest source of fatty acids in the body, and 15% to 30% of those lipids are essential fatty acids (EFAs) and LC-PUFAs. Nerve cell function, membrane fluidity, neuron membrane dynamics, and the subsequent receptors, transporter, and neurotransmitter function are profoundly affected by the lipids that we consume through diet and supplementation. Considerable research including randomized controlled trials now demonstrates the role and efficacy of EFAs in numerous psychiatric disorders.

Several probable mechanisms may explain the link between EFAs and depression. EFAs can modify 5-HT receptors, affect serotonin and dopamine metabolism, lower monoamine oxidase B, modulate cytokine production, and enhance signal transduction. The composition of cell membranes, neurotransmission, and prostaglandin metabolism are all affected by the amounts of EFAs; and while clinical trials are few, there is substantial laboratory and observational evidence of the correlation between low essential fatty acid levels and depression.

According to the *American Journal of Psychiatry*, depression is one of the 10 most frequent indications for the use of complementary and alternative medicine.[1] While many nutraceuticals and botanicals have published evidence to their benefits, omega-3 PUFAs are among the more commonly used.[2]

Epidemiologic studies in several countries suggest that decreased omega-3 fatty acid consumption correlates with increasing rates of depression. One researcher who studied the relationship of fish consumption and the incidence of depression correlated the annual incidence of major depression per 100 people in 9 countries with the consumption of fish.[3] He found a high incidence of depression in countries with low fish consumption and a lower incidence of depression in countries with high consumption. For example, New Zealanders have an annual fish consumption of about 40 pounds and an annual incidence rate of depression of 5.8%. Japan, on the other hand, with a fish consumption of almost 150 pounds per year, had the lowest incidence of major depression, at 0.12%.

This group also demonstrated that prevalence rates for bipolar affective disorder rise when the annual fish intake falls below 75 lbs of fish per person annually. In Taiwan, for example, there is a 0.04% rate and fish intake is 81.6 lb per person per year as compared with Germany, where the rate is 6.5% at 27.6 lb of fish per person annually. In a survey of 3204 Finnish adults, infrequent fish consumption was associated with depression in women and, although not statistically significant, a trend was seen in men.[4] Fish intake also appears to have an influence on suicide, with a reduced risk of death from suicide in individuals with daily fish consumption.[5]

In a group of 20 patients with moderate to severe depression, the relationship was studied between depression and levels and ratios of omega-3 and omega-6 fatty acids in plasma and erythrocyte phospholipids.[6] Using two commonly accepted scales and methods of evaluating depression, researchers found a significant correlation between the ratio of phospholipid arachidonic acid to EPA (eicosapentaenoic acid) and the severity of depression. The greater the omega-6 to omega-3 ratio, the greater the severity of the depression.

In 2010, researchers found that patients with major depressive disorders exhibited significantly lower erythrocyte docosahexaenoic acid (DHA) composition compared with healthy controls. Individuals with bipolar disorder appeared to have an even lower DHA level. [7]

Other investigations have confirmed that a high concentration of blood plasma DHA levels has been linked to an increase in serotonin turnover, which resulted in lower rates of depression and even suicide. Some science has suggested that switching to a cholesterol-lowering diet may also result in the reduction in measures of depression, although not all studies demonstrate this.[8] It appears that there is a consistent

positive association between depression and coronary heart disease and heart attacks.[9] These conditions may in fact carry a common link, that of elevated cholesterol. Since there is such a strong correlation between depression and coronary artery disease, and a predictive correlation between elevated cholesterol and heart disease, elevated serum cholesterol may also predict increased depression.

Depression secondary to alcoholism is quite common and occurs in up to 59% of alcoholics. Alcoholism is certainly a complicated illness, with social, psychological, hereditary, physiological, and physical factors to consider. We also know that alcohol is a prooxidant that leads to increased lipid peroxidation. A consequence of increased lipid peroxidation may be a decrease in the concentrations of the more highly unsaturated types of fats, such as PUFAs. Several studies have demonstrated that chronic alcohol abuse depletes long-chain omega-3 polyunsaturated fatty acids from neuronal membranes.[10] It is hypothesized that the subsequent effect on the membranes may promote the development of depression.

Interestingly, higher intakes of fish did not have a protective role against depression in more severe situations and have not been associated with a lower risk for suicide in Japan. However, women in Japan with very low intakes of fish did have an increased risk of suicidal death.[11]

As of August 2011, four meta-analyses have examined the results of randomized controlled trials of omega-3 supplements for unipolar major depression.[12–15] They all concluded that omega-3 supplements have a potential for treating depression. However, these meta-analyses included studies that were small trials and of different EPA-DHA formulations, ratios, and dosages. The most promising results within the meta-analyses are from the Peete-Horrobin trial in 2002, the Nemets-Stahl trial of 2002, and the Su-Huang trial of 2003 discussed below.

A search of the literature examining the therapeutic efficacy of essential fatty acids for depression was published in 2006.[16] One double-blind, placebo-controlled RCT examined the use of omega-3 fatty acids in 30 men and women.[17] The intervention group received 9.6 g of omega-3 fatty acids from fish oil in addition to their standard pharmacological treatment for 4 months. A Kaplan-Meier survival analysis found that the fish oil group had a significantly longer period of remission than the placebo group and performed better than the placebo group in other outcome measures. Three case control studies of adults with major depression and nondepressed healthy adults all showed a significant difference in levels of omega-3s between depressed and nondepressed adults.[18–20] Similarly, a review article suggested that DHA is beneficial for depression as well as several other conditions.[21] A second review article discussed the effects of dietary intake patterns on fatty acid balance and potential effect on mood.[22]

Three intervention studies have been done since the initial literature review that concluded in 2001 and do provide support for the effectiveness of EPA, or a combination of EPA with DHA. In a study of 28 patients with major depression, 9.6 g/day showed significant improvement compared with the placebo group.[23] In a study of EPA, 1 g/day demonstrated significant improvement in two different depression scales compared with placebo and no further improvement was seen in higher doses of EPA than 1 g/day.[24] A combination of EPA or placebo and conventional pharmaceutical antidepressant treatment in unipolar depression demonstrated that individuals in the EPA group had significantly better effects by the third week. The efficacy of omega-3 supplementation as an antidepressant treatment in individuals with major depressive disorder was also seen in a study published in 2002.[25] Twenty-two individuals received 2 g/day of EPA in addition to standard antidepressant medication, and were compared with individuals who just took their standard antidepressant medication and a placebo. In this 3-week study with participants who had treatment-resistant major depression, EPA demonstrated an effect on depressed mood, insomnia, and feelings of guilt and worthlessness.

In a 2012 study, omega-3s along with a prescription antidepressant, citalopram, was conducted over a 9-week period.[26] The objective of this study was to explore combination therapy by using citalopram and omega-3 fatty acids versus citalopram plus placebo in the primary treatment of individuals with major depressive disorder. Forty-two subjects received 2 g/day containing a blend of 900 mg EPA, 200 mg DHA, and 100 mg of other omega-3 fatty acids, twice daily, in addition to citalopram, versus the other group who received an olive oil placebo plus citalopram. The omega-3 plus citalopram combination therapy provided significantly greater improvement in Hamilton Depression Rating Scale (HAM-D) scores beginning at week 4 and continuing throughout the duration of the study. While the combination therapy achieved a decrease in signs and symptoms of major depression, it did not improve the onset of response time.

In an 8-week, single-blind, placebo-controlled trial, peri- or postmenopausal women with depressive disorders and hot flashes were given 6 g/day of EPA and DHA. The response rate was 70% and a decrease of 50% or more on the Montgomery-Åsberg Depression Rating Scale (MADRS).[27]

The efficacy of omega-3 supplementation for major depression was documented in another recent randomized, controlled trial of 8 weeks in which 432 participants with major depression were randomized to 1050 mg of DHA or a matched placebo.[28] There was only a small statistical trend toward superior benefits in major depression with the DHA over placebo. However, there was clear benefit of DHA in patients with major depression and anxiety disorders. This has been the largest randomized, controlled trial to date to study the efficacy of omega-3 supplementation for major depressive disorder.

A study of DHA only, on the other hand, with a dose of 2 g/day of DHA or placebo in 36 depressed participants, found no significant difference between the DHA and the placebo group. There was, however, a better overall response rate in the DHA group.[29]

Contrary to some of the negative results with DHA, the antidepressant effect of DHA was examined in 35 depressed adult participants (46% women average age of 42 years) in which the individuals were randomized into one of 3 groups: 1 g/day of oral DHA, 2 g/day of oral DHA or 4 g/day of DHA. Using the HAM-D, the response rates of 50% or more was 83% for 1 g/day , 40% for 2 g/day and 0% for 4 g/day. The two lower dose DHA groups had a significant decrease in the

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HAM-D scores, demonstrating that lower doses of DHA may be an effective intervention for depression. [30]

A very specific population at risk of developing depression is that of individuals who experienced a recent acute myocardial infarction (AMI). A growing body of evidence suggests a link between psychosocial factors, cardiovascular risk, and prognosis in patients with acute heart attacks. Twenty percent of individuals with AMI have a history of major depression, and 70% to 80% report anxiety. Omega-3 fatty acids are one of the potential factors that link these mood disorders as well as cardiovascular complications. This link has caused researchers to take aim at assessing whether early supplementation of omega-3 fatty acids affects depression and anxiety in participants with AMI and no previous history of mental health disorders. In late 2013, a study was published that enrolled 52 participants with AMI.[31] They were randomized to 1 g/day of fish oils plus standard AMI therapy or control group plus standard AMI therapy. The test scores for depression and anxiety were significantly lower for the fish oil group and provide evidence that intervention with fish oils in AMI patients may decrease their anxiety and depression post MI.

It remains quite unclear as to the optimal dosing and ratios of EPA/DHA in the prevention and treatment of depression. Successful studies have used doses ranging from 1 g/day to 9.6 g/day. Some studies have used high-EPA formulas, while others have used DHA-dominant formulas, in low and high doses. The most benefit has been for pure EPA and EPA-DHA mixtures; however, at least one study had benefits with the low doses of DHA at 1 g or 2 g/day.

A 2013 trial sheds light on this issue.[32] This single-center, randomized, double-blind, placebo-controlled, multi-arm, parallel-group trial compared the efficacy of EPA versus DHA as adjuvants to maintenance medications for the treatment of mild to moderate depression. Eighty-one mild to moderately depressed individuals randomly received either 1 g/day of EPA or DHA or placebo for 3 months. The primary outcome was the final score of the HAM-D. Participants in the EPA group showed a significantly better reduction in the score as compared with the DHA and placebo groups. There were also more individuals with a 50% response to treatment in the EPA group (6) and none in the DHA or placebo group

A comparison study looked at the omega-3 fatty acid EPA and fluoxetine (a prescription antidepressant) separately and in combination, in individuals with major depression.[33] Sixty participants with major depressive disorder were randomly assigned to receive daily either 1000 mg EPA or 20 mg fluoxetine or combination for 8 weeks. EPA plus fluoxetine combination was significantly better than fluoxetine or EPA alone after the 4th week of treatment. Fluoxetine and EPA appeared to be equally effective in controlling depressive symptoms. Response rates (> or = 50% decrease in baseline HAM-D) were 50%, 56%, and 81% in the fluoxetine, EPA, and combination groups, respectively.

In May 2014, researchers published a study in which they conducted a meta-analysis on the usage of omega-3 fatty acids for the treatment of depression. They specifically looked at randomized, controlled trials with omega-3 PUFAs for the treatment of depression and then analyzed the outcomes among the participants in these studies.[34]

The meta-analysis considered studies that took place until August 2013 and included people diagnosed with major depression as well as those who had depressive symptoms but were not officially diagnosed. Both these groups of individuals had significant improvements with omega-3 PUFA supplementation. Formulations with mostly EPA (rather than DHA) were more effective.

Another motivation to use omega-3s for depression is that antidepressants can have significant side effects and, even more worrisome in younger people, an increase in suicides. One group of researchers was motivated by this fact and divided 400 participants aged 15 to 25, all of whom had a major depression diagnosis, with one group receiving cognitive behavioral therapy (CBT) and the other group 1.4 g/day of omega-3 fatty acids plus CBT for 12 weeks. The study found that omega-3 PUFAs provided a significant antidepressant effect, and the authors concluded that they should be used as a "first-line therapy" in young people with major depression.[35]

A meta-analysis in 2013 highlighted the fact that many studies have cited low levels of omega-3 fatty acids among individuals with depression. They assert that early studies of omega-3 formulations for depression found benefits, but then other studies were not demonstrating significant results. They postulate that the reason for this is due to studies that have DHA-dominant formulations and emphasize the importance of EPA-dominant formulations to achieve efficacy.[36]

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Dr. Tori Hudson graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in many capacities. She is currently clinical professor at NCNM and Bastyr University, has been in practice for over 31 years, and is medical director of the clinic A Woman's Time in Portland, Oregon. She is the author of the book *Women's Encyclopedia of Natural Medicine*; a contributing author to several books, including the *Textbook of Natural Medicine*; and director of research and education for Vitanica, a supplement company for women. She is a nationally recognized author, speaker, educator, researcher, and clinician.

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ConsumerLab.com Tests Reveal Best and Worst Magnesium Supplements

Magnesium supplements have become extremely popular, surpassing even calcium among frequent users of supplements. However, recent tests by ConsumerLab.com reveal that not all magnesium supplements contain what they claim – and higher cost doesn't mean higher quality. In fact, some supplements that passed ConsumerLab.com's tests cost just a few cents per dose, while others costing *20 times* as much failed. One widely promoted and relatively expensive product, for example, contained only 61.5% of its listed magnesium. Among the 18 products selected for review, 3 failed testing and 15 were approved for quality.

Magnesium is now the most popular mineral supplement and the sixth most popular supplement overall, according to a recent survey by ConsumerLab.com of more than 10,000 supplement users, with use increasing to 43.1% of respondents compared with 38.1% last year.[1] Sales of magnesium supplements increased 16.7% in 2014, according to Nutrition Business Journal, reaching $680 million. While magnesium deficiency is rare, supplements may be helpful for conditions such as constipation, heartburn, migraines, and menstrual pain and is often touted for leg cramps.

ConsumerLab.com tested popular magnesium supplements to determine whether they contained the amount of magnesium and/or other key ingredients claimed on the label, were not contaminated with heavy metals, and, if in tablet form, were able to properly break apart.

The test results and quality ratings appear online in ConsumerLab.com's new Magnesium Supplements Review.[2] The report covers 18 products selected by ConsumerLab.com and 17 others which passed the same tests in ConsumerLab.com's voluntary Quality Certification Program. Also included are 2 products similar to one that passed testing but which are sold under different brand names. The report discusses the evidence for/against using magnesium for a variety of conditions and the different forms of magnesium (such as citrate, chloride, and oxide), and explains which forms are better absorbed and less likely to cause side effects. Information about dosage and potential drug interactions is also presented.

The following products are included in the report: Bayer Citracal Slow Release 1200, The Vitamin Shoppe Calm Zone Magnesium, Caltrate 600+D Plus Minerals, Cardiovascular Research Ltd. Magnesium Taurate, Carlson Chelated Magnesium, ChildLife Liquid Calcium With Magnesium, Country Life Bone Solid, Doctor's Best High Absorption 100% Chelated Magnesium, Finest Nutrition [Walgreens] Magnesium, GNC Calcium Plus 1000, Jarrow Formulas Bone-Up, Jarrow Formulas MagMind, Jigsaw Health Magnesium w/SRT, Kirkland Signature (Costco) Calcium Citrate Magnesium and Zinc, Kirkland Signature [Costco] Magnesium Citrate, LifeExtension Magnesium Caps, Nature Made Calcium Magnesium Zinc, Nature's Bounty High Potency Magnesium, Nature's Way Alive Calcium Bone Formula, NutriCology Magnesium Chloride Liquid, Nutrilite Cal Mag D Advanced, PipingRock.com Magnesium Chloride, Pure Encapsulations Magnesium (Glycinate), Rainbow Light Food Based Calcium, ReMag Magnesium Solution, Rexall Magnesium, Shaklee Osteomatrix, Solgar Magnesium Citrate, Source Naturals Magnesium Malate, Spring Valley [Walmart] Magnesium Citrate, Trace Minerals Research ConcenTrace, TwinLab Magnesium Caps, USANA Active Calcium, and Vitacost Magnesium Ultra.

Founded in 1999, ConsumerLab.com is a leading provider of consumer information and independent evaluations of products that affect health and nutrition. Membership to ConsumerLab.com is available online and provides immediate access to reviews of more than 1000 products from over 400 brands. The company is privately held and based in Westchester, New York. It has no ownership from, or interest in, companies that manufacture, distribute, or sell consumer products.

Notes

1. Use of magnesium and probiotics rise, multivitamins and weight loss supplements fall, according to ConsumerLab.com survey [online article]. ConsumerLab.com. Feb. 28, 2015. https://www.consumerlab.com/news/Use%20of%20Magnesium%20and%20Probiotics%20Rise/2_28_2015.
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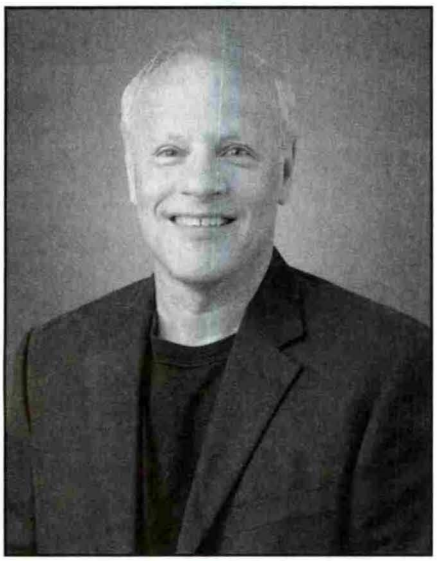

The $50,000 Physical

In a recent editorial in the *Journal of the American Medical Association*, a physician related the story of his 85-year-old, reasonably healthy father who had relocated to an assisted-living facility and visited his new primary care physician for a "checkup."[1] On the routine physical examination, the doctor palpated the patient's abdomen and noted that the aorta appeared to be too prominent. The patient was therefore referred for an abdominal ultrasound, in order to rule out an aortic aneurysm. The ultrasound demonstrated a normal aorta, but it also revealed a suspicious lesion around the head of the pancreas, so a CT scan was recommended. On the CT scan, the pancreas was found to be normal, but a lesion strongly suggestive of hepatocellular carcinoma was seen on the liver. The patient therefore underwent a liver biopsy, to confirm the diagnosis and to determine whether an effective treatment was available. The liver biopsy revealed that the lesion was not cancer. Rather, it was a hemangioma, which bled profusely during the procedure, requiring transfusion of 10 units of blood and 7 days of hospitalization. Another complication of the biopsy was severe pain requiring treatment with morphine, which resulted in urinary retention and the temporary insertion of a urinary catheter. The total hospital bill for this fiasco was $50,000.

The author of this report acknowledged that, after the doctor's initial examination, every test and every intervention was medically appropriate. And yet, these "appropriate" tests and interventions nearly caused a healthy 85-year-old man to bleed to death, caused him great physical pain and emotional trauma, and cost the medical system a large amount of money. The author also rightly pointed out that the only way this catastrophic outcome could have been avoided would have been if the doctor had not conducted the initial physical exam. As one of my medical school professors liked to say (only half facetiously), "If you don't take a temperature, you don't have to worry about a fever."

To be sure, certain aspects of routine preventive medical care have value, as noted below. However, for an asymptomatic, healthy 85-year-old man, expert opinion is that a physical exam could reasonably be limited to measuring blood pressure and assessing body mass index. Moreover, a meta-analysis of 14 randomized trials (including a total of 182,880 participants) found that, in adult populations unselected for disease or risk factors, undergoing routine health check-ups did not reduce overall morbidity or mortality. To the contrary, one study found that having regular checkups increased by 20% the number of new diagnoses and increased the number of people with self-reported chronic conditions.[2]

Despite the evidence that routine physical exams and general checkups are not beneficial, patients continue to show up for them and doctors continue to perform them. No doubt many continue this ritual out of fear that some serious illness might be overlooked until it is too late for treatment to be effective. However, the evidence seems to indicate that whatever benefits are obtained from annual checkups are counterbalanced by the harm done from following up on false-positive findings.

We certainly should do our best to eat healthful foods, avoid tobacco and other toxins, get regular exercise, maintain a positive attitude, and engage in other lifestyle behaviors that may improve health and prevent chronic disease. And we should undergo screening tests at appropriate intervals to detect conditions for which early intervention may be beneficial. These would include breast exams, Pap smears, colonoscopies, dental exams, blood pressure measurements, blood chemistry and hematology, urinalysis, and assessment of cognitive function. However, with regard to the annual physical exam that has been a ritual for so many Americans, the evidence indicates that patients would do just as well if they stayed home.

As a nation, we spend more on health care per capita and as a percentage of gross domestic product than does any other nation in the world. Yet, despite these massive expenditures, we rank dead last among 17 affluent nations with respect to various measures of overall health. As we continue to struggle, both personally and as a society, with the enormous and growing costs of medical care, it is imperative that we reevaluate all of our practices, and begin phasing out those for which the benefits do not outweigh the harms and for which the benefits do not justify the costs. I, for one, will do my part to help to stem the burgeoning health-care costs by staying away from the doctor as much as I can.

Alan R. Gaby, MD

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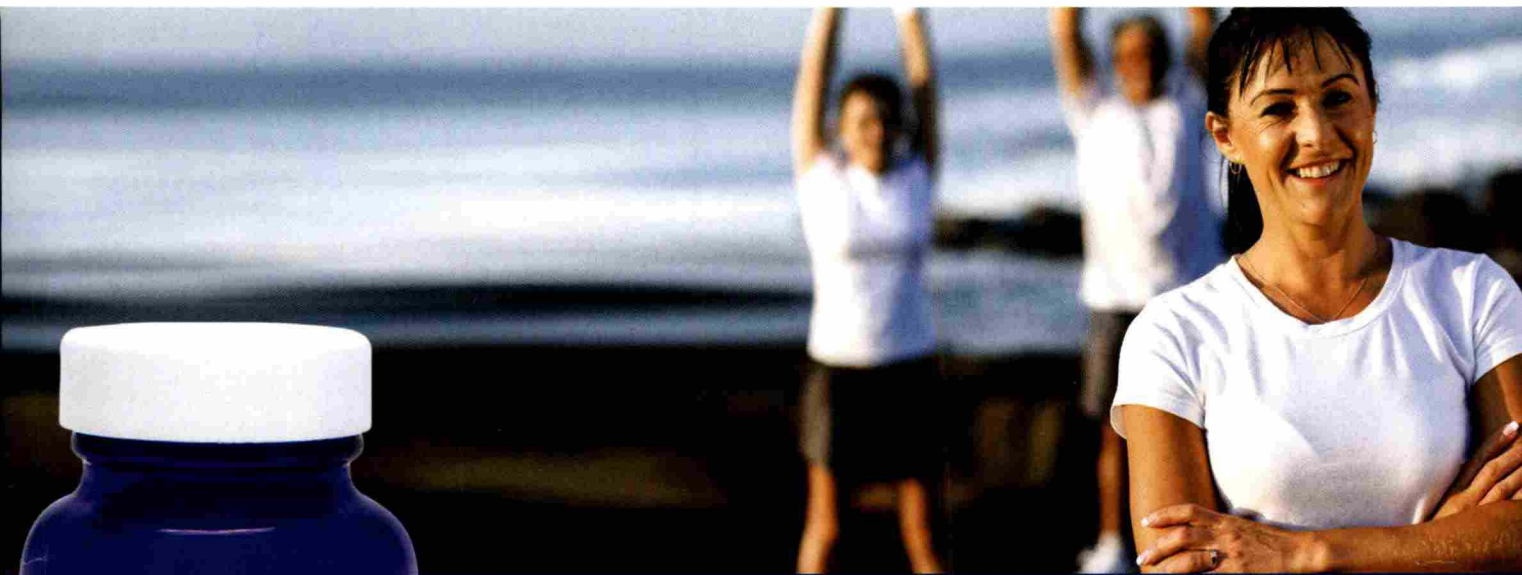

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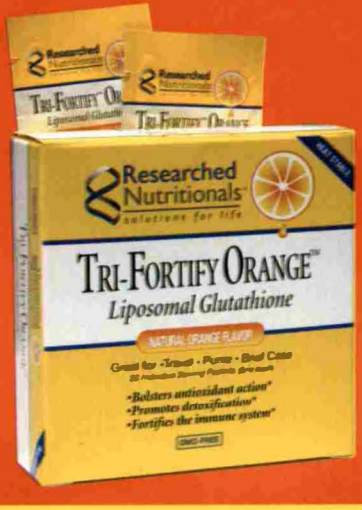

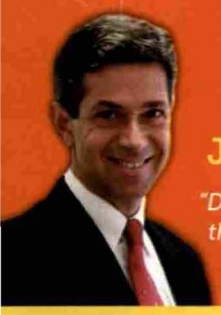

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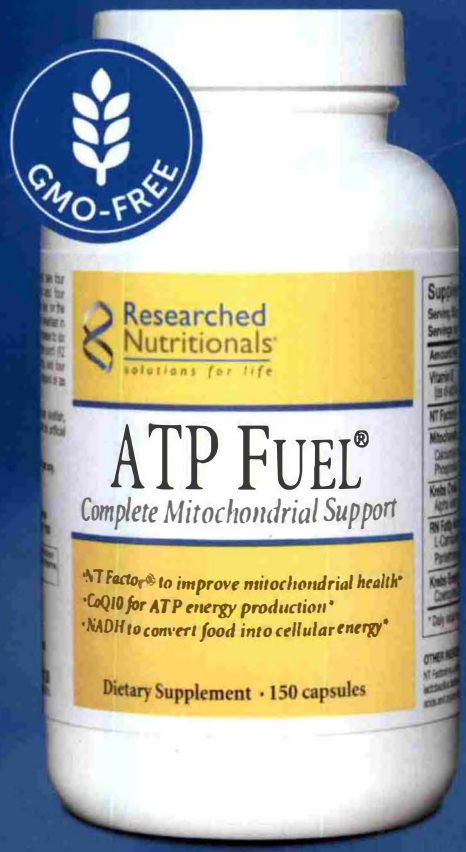

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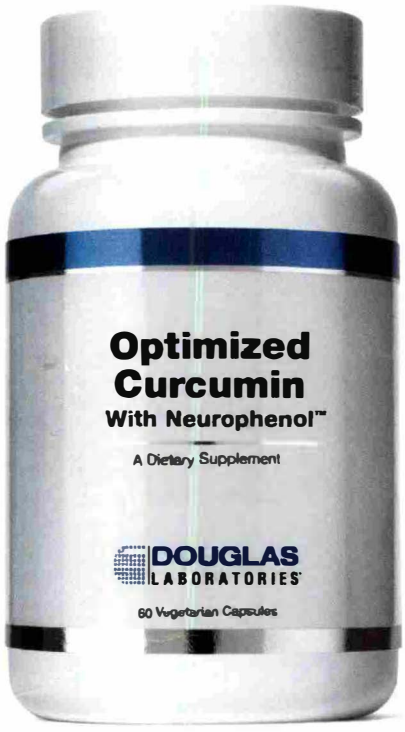

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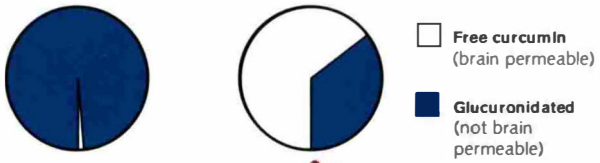

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