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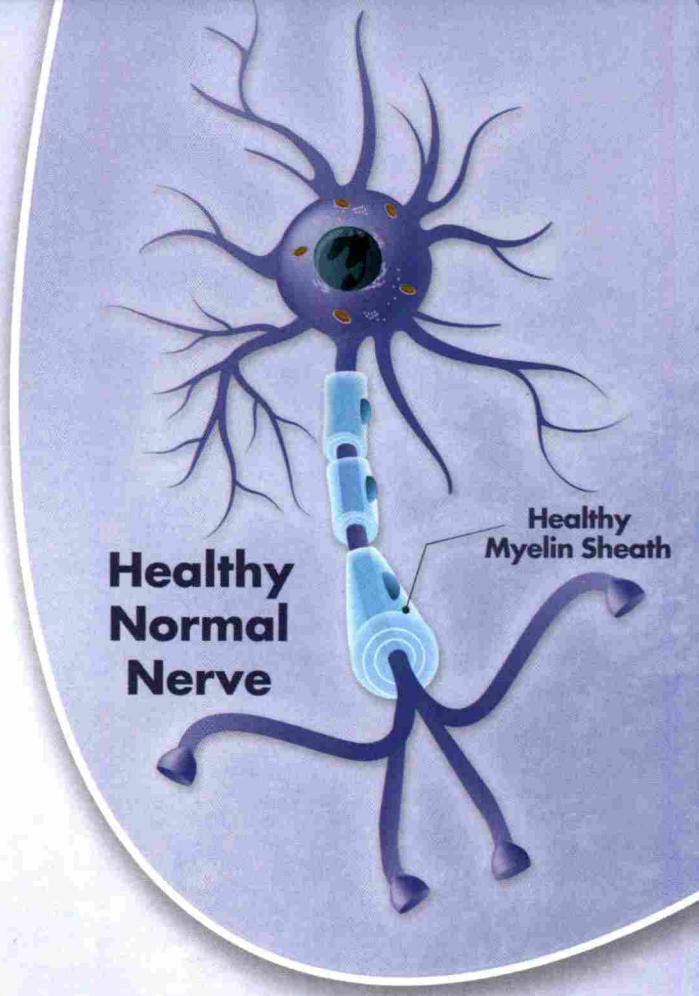

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From the Publisher

Ralph Moss's *Cancer Therapy*: 20 Years Later

In the mid 1980s, the "War on Cancer" had been under way for nearly 15 years but without much to show for itself. While conventional chemotherapy had been having measurable success with certain leukemias and lymphomas and childhood cancers, cancer treatment had not had broad success, particularly with gastrointestinal malignancies, brain tumors, and most cancers that had metastasized. More than any other reason, patients were introduced to and sought out "alternative medicine" to treat cancer, particularly when their cancer treatments were failing. Unconventional cancer therapies were especially developing since World War II, and by the late 1970s, clinics offering such treatments were facing increasing scrutiny by medical authorities. Perhaps the primary reason that a physician faced medical board sanctioning was promoting and providing unproven cancer treatment. A growing number of physicians and patients were becoming incensed that they were being denied access to alternative cancer treatment in the US, forcing them to seek such care in Tijuana (Mexico) and elsewhere abroad.

continued on page 8 ➤

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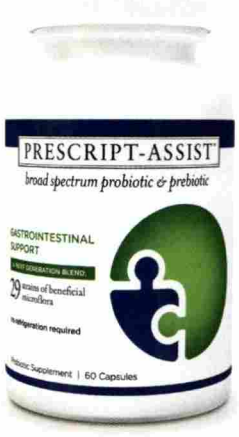

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[1] Pennisi, E. (2011). Body's Hardworking Microbes Get Some Overdue Respect. *Science, 330* (December 2010), 1619.

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Letter from the Publisher

➤ continued from page 6

In addition, in the early 1980s, patients with HIV and AIDS were demanding access to experimental treatments on an expedited basis from the FDA. Consequently, a contingent of representatives and senators demanded that Congress investigate alternative cancer treatment. The Congressional Office of Technology Assessment (OTA) embarked on a major study of alternative cancer treatment in 1986. While the OTA brought in university faculty and skeptics who opposed alternative cancer treatment, a number of proponents of alternative medicine were invited to participate. I recall this well, as I was a participating member in the study from 1987 to 1989. Dr. Andrew Weil was a strong voice for employing nutrition and herbals in treating cancer. There was a circle of alternative cancer advocates who strongly supported the right for obtaining alternative cancer care; among those championing access to these treatments were Frank Wiewel, Bob Houston, Pat McGrady, Marcus Cohen, and Ralph Moss. As one might imagine, the skeptics in the study were disdaining treatments such as Burton's Immune Augmentative Therapy, Kelly's diet and pancreatic enzyme treatment, as well as Gerson's juicing diet and coffee enemas. The OTA report gave high grades to psychological approaches such as meditation, healing treatments including acupuncture and chiropractic, and "prudent" nutrition. Unfortunately, the report generally gave nutritional supplementation and herbals a weak grade, and frankly degraded well-known unconventional cancer protocols. Amazingly, members of Congress did not buy into the negative bias of the report and voted overwhelmingly in 1990 to establish the first Office of Complementary and Alternative Medicine. In the ensuing years, the NIH expanded a small, poorly funded office into the Center of Complementary and Alternative Medicine. Additionally, the National Cancer Institute was asked to fund studies of promising alternative cancer therapies. Several years later, in 1994, DSHEA was passed, ensuring free access to nutritional supplements, blocking FDA interference with innovative alternative cancer treatments.

The late 1980s through the early 1990s was a banner time for patients seeking alternative cancer treatments. In 1992, Ralph W. Moss, PhD, author of *The Cancer Industry*, published *Cancer Therapy: The Independent Consumer's Guide to Non-Toxic Treatment & Prevention*. Readers of the *Townsend Letter* are familiar with Moss through his many years of writing the "War on Cancer" column. Moss has been a valuable resource for doctors and patients over the past 25 years, offering a detailed and personalized report for treatment recommendations based on the patient's cancer. In addition to examining conventional and alternative options for management of the cancer in the US and abroad, Moss suggested investigational studies that patients might be able to participate in. Note that in the earliest years of this work, there was no availability for Internet searches.

continued on page 10 ➤

Cancer Treatment and Prevention

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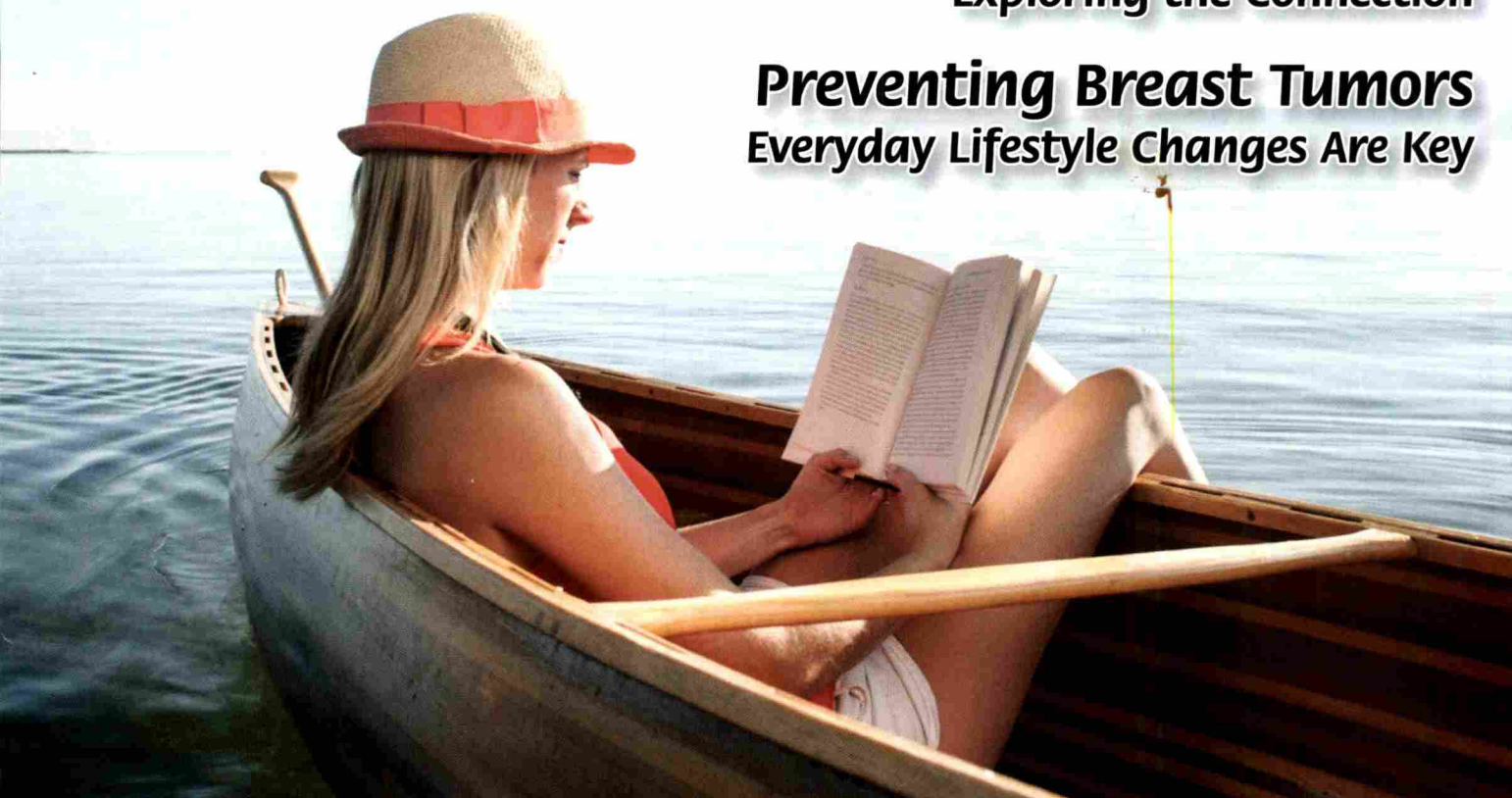
Exploring the Connection

Preventing Breast Tumors
Everyday Lifestyle Changes Are Key



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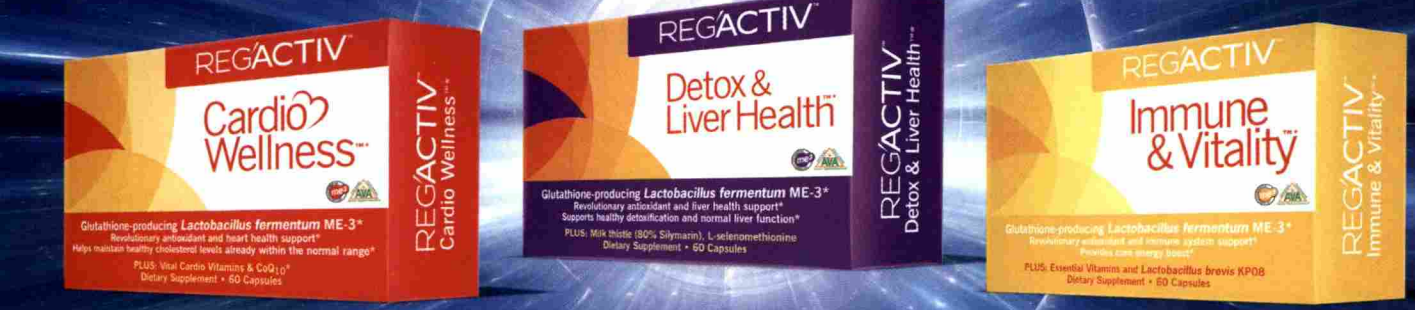

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Letter from the Publisher

➤ continued from page 8

Moss's *Cancer Therapy*, last updated in 1998, remains a valuable resource for physician and patient. Although the referenced studies are primarily from the 1970s to 1990s, the evidence for effectiveness of vitamins, minerals, herbs, diets, immune boosters, and less toxic drugs provides a good primer. Too often, patients and, to a lesser degree, physicians, are not able to get a reasonable sense of the background behind why supplementation and diet are of value. More concerning is the problem that patients make use of a limited number of alternative cancer options; too frequently, the patient latches on to a few supports advised by friends or the Internet. Moss's book lays out a broad scope of potential interventions with suggestions for resources – a useful tool given the confusing advertising rampant on the Internet.

We are all familiar with the anti-inflammatory effect of curcumin found in the spice turmeric. Researchers in India determined that curcumin not only reduced the progression of tumor cell development, but had a particularly strong effect in retarding abnormal lymphocyte activity.[1] Curcumin, prepared as a poultice, has been shown to reduce the size of inflamed skin lesions, potentially reducing skin cancers.[2] Moss's discussion of the herb astragalus reminds us of its important role in lessening the harsh effects of chemotherapy. Astragalus reduces the risk of various chemotherapy agents' causing abnormal liver functioning. Given the general safety of astragalus, this hepatic protective effect would be a very useful ancillary treatment.[3]

The anti-inflammatory activity of fish oil has been well recognized in supporting arthritic inflammation and reducing cardiovascular dysfunction. Moreover, fish oil appears to be helpful in reducing tumor size. In experiments where mice were given chemicals capable of initiating colon cancer, those fed diets high in omega-3 fish oil, compared with those fed omega-6 safflower oil, had the lowest development of new cancer.[4] More importantly, fish oil appears to inhibit weight loss and cachexia in cancer treatment.[5]

The use of medicinal mushrooms, acknowledged to be helpful in deterring tumor progression, is generally underutilized. Shiitake mushrooms are supportive to the immune system. Japanese scientists have isolated a fraction of the shiitake mushroom, lentinan, which appears to enhance the anticancer activity of shiitake. In Japan, lentinan has been combined with chemotherapy to markedly increase the benefit of chemotherapy. Lentinan lengthened survival of patients with advanced cancers. The medical literature supporting the use of lentinan is extensive.[6]

continued on page 15 ➤

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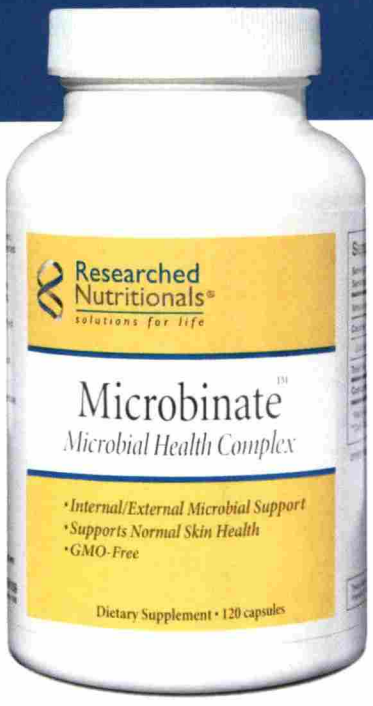

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IN THIS ISSUE August/September 2015 | #385/386

IN THIS ISSUE: A Cancer Vaccine? (43); Yogurt Against Heavy Metals (40); Preventing Breast Tumors (109); Cancer and Spirochetes (52); Prostate Cancer's Impact on Sex (94)

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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.

Letter from the Publisher

➤ continued from page 10

Moss considers numerous chemical and drug therapies that have potential anticancer effectiveness, including anticoagulants, benzaldehyde, butyric acid, DMSO, enzyme therapy, hydrazine sulfate, cimetidine, urea, and vaccine therapy. His review of "undocumented therapies" introduces the reader to Essiac tea, Naessens's frequency treatments, and Burzynski's antineoplastons.

Moss's *Cancer Therapy* remains a useful reference 20 years later.

Irene Alleger, Former Editor of the *Townsend Letter*

Irene Alleger, former editor of the *Townsend Letter*, passed in June at the age of 88. Irene played a vital role in the early years of the publication during the mid-1980s when publishing was still being done from typewritten galleys, and magazine pages were photographed before being printing. Unlike the current magazine, Irene was singlehandedly in charge of editing a great number of articles; the early *Townsend Letters* were typically 140 pages. Not unremarkably, the editing was excellent; not only were typos and spelling errors essentially nonexistent, but Irene was frequently asked to rewrite poorly written articles by doctors who had deficient writing skills. Irene's commitment to the magazine editing was unwavering – not once in 15 years were any of the deadlines missed.

In addition to editing, Irene was single-minded and resolute in writing editorials that decried the abuses of the medical establishment, criticized the callous materialism of the pharmaceutical companies, and challenged the abuse that medical boards foisted on integrative doctors. After resigning from her editing duties, Irene served as a book reviewer, connecting the *Townsend Letter* with the publishing houses. Prior to serving as the magazine's editor, she served for many years as my medical receptionist and assistant. Irene advocated strongly for patient access to integrative medicine and helped patients achieve optimal health care.

Irene's work was very important to the fledgling *Townsend Letter* and spearheaded its growth through the past 30 years. She was a good friend and will be greatly missed.

Cannabinoids: The New Mainstream Medicine?

The recent legislation authorizing free access to marijuana in Oregon now enables its citizens to join those legally purchasing it in Colorado and Washington State. In more than 20 other states and the District of Columbia, medical use of marijuana has also been legalized in the past decade. Despite the fact that marijuana remains classified as a Schedule 1 (prohibited) drug, the DEA and the US Justice Department have recently taken a more hands-off approach to the personal use of marijuana. It is remarkable, in Washington State, to observe billboards promoting retail stores selling "bud." While "recreational" sales for marijuana are booming, medical use is also dramatically increasing, creating concerns regarding what type of marijuana should be used. From a basic standpoint, the division is between the more psychoactive component, THC (tetrahydrocannabinol), and the more "healing" component, CBD (cannabidiol). The major marijuana sales are for *Cannabis sativa*, having a greater percentage of THC, and *Cannabis indica*, having the higher concentration of CBD. For all the distinctions, analytic quality control is very limited; there are labs claiming to assess THC/CBC concentrations, but these firms are not USP approved. In Washington State, the major concern is that the tax authority has oversight to ensure that plant cultivation and sales are regulated and taxed, not to ensure quality control. Hence, medical response to marijuana products may vary greatly. Still there is growing consensus that marijuana, particularly CBD marijuana, is important in ameliorating the adverse effects of cancer treatment and may be important in enhancing the effectiveness of cancer treatment (see Sean Devlin's article in the Aug./Sept. 2014 *Townsend Letter*).[7] The potential role for using THC and CBD on treating glioblastoma has been reported.[8] A clinical observation of mine was a noted reduction in both grand mal and petit mal seizures in a 16-year-old male who had diagnosed glioma. What was particularly remarkable in my patient was a noted reduction in the size of the glioma following 6 months use of THC/CBD oil.

In the current issue, Shelley White writes about the medical uses of cannabis in the treatment of Lyme disease and related conditions. White suffered with major Lyme disease disability and actively followed an aggressive treatment protocol for 1 year. Nevertheless, her condition only improved slightly and she eschewed additional medical support. Instead, she initiated active use of marijuana, both THC and CBD content. Her cognitive dysfunctioning improved dramatically with marijuana use. Based on her experience, she has written a new book: *Cannabis for Lyme Disease and Related Conditions: Scientific Basis and Anecdotal Evidence for Medicinal Use.*

Should we expect to see a broadening role for marijuana in many other conditions?

Jonathan Collin, MD

Notes

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◆

National College of Natural Medicine Receives $3,092,898 for NIH Research Grants

The National Institutes of Health, through the National Center for Complementary and Integrative Health (NCCIH), has awarded $3,092,898 to the Helfgott Research Institute at the National College of Natural Medicine (NCNM) for two five-year complementary integrative health (CIH) research grants.

The new grants will provide funding for studies involving mindfulness-based stress reduction for people with multiple sclerosis, and clinical research training for naturopathic doctors and Chinese medicine practitioners, as well as training in naturopathic and Chinese medicine modalities for conventional medicine researchers.

Said NCNM President David J. Schleich about the new funding: "The School of Research & Graduate Studies at NCNM and our Helfgott Research Institute are growing at an unprecedented pace – because there is a need. With the increasing use of complementary and alternative medicine, high-quality rigorous research is essential so that CIH therapies can be accurately evaluated to help keep the public informed. We are honored to be able to partner with our esteemed colleagues at OHSU and UW on these important projects to grow this critical field of research."

The K23 Mindfulness-Based Stress Reduction for Multiple Sclerosis (Feasibility, Durability and Clinical Outcomes) program is being undertaken with Oregon Health & Science University (OHSU). The Building Research across Inter-Disciplinary Gaps (BRIDG) T90/R90 Clinical Research Training program in Complementary and Integrative Health is under way in collaboration with the University of Washington (UW) in Seattle. The two NCNM research programs have been awarded a total of $672,550 and $2,420,348 respectively. NCNM and its Helfgott Research Institute have received eight NIH awards totaling $6,046,183 since 2002.

"The NCCIH awards are gratifying – not only because of the recognition from our federal government for the value of our research, but also for furthering our ability to help NCNM students develop the skills they need to contribute to the evidence-base of natural medicine," Schleich said.

K23 Mindfulness-Based Stress Reduction for Multiple Sclerosis Program

Multiple sclerosis (MS) is the most common neurological condition affecting young adults in the US. MS symptoms are diverse and unpredictable, and include diminished mobility, chronic pain, fatigue, depression, anxiety, and cognitive impairment. Studies have shown that psychological stress can exacerbate MS symptoms and trigger relapses.

While mindfulness-based stress reduction (MBSR) clinical trials have demonstrated improved health conditions for many patient populations, few trials have been applied to people with neurological impairments. A recent study found that participation in a stress-reduction trial reduced the frequency of new lesion development in MS, suggesting that stress management might not only improve symptoms but also modify the disease progression.

The threefold aim of this program is to conduct research that will evaluate the feasibility of MBSR for people with multiple sclerosis, assess the durability of outcomes over a 12-month period, and understand which postintervention activities and behaviors might support or inhibit sustainability.

NCNM researchers will introduce MBSR to study participants as an 8-week program consisting of weekly 2-hour classes in meditation, breath work, yoga, self-reflection and awareness.

T90/R90 BRIDG Clinical Research Training Program

The primary goal of the BRIDG program is cross-training promising investigators to translate CIH (formerly known as complementary and alternative medicine) concepts into testable, multidisciplinary research hypotheses and to apply translational research methods to CIH-oriented research. Recognizing that research in CIH requires a multidisciplinary approach, NCNM and UW have combined their expertise in research, clinical care, and CIH to create an immersive clinical research training program that will foster collaboration and respect among a variety of medical and research disciplines.

The program integrates doctoral-level CIH health-care providers (e.g., doctors of naturopathic, chiropractic, and acupuncture and Oriental medicine) and conventionally trained researchers from biomedical and public health disciplines (e.g., medical doctors, doctors of public health, PhDs).

The R90/NCNM component of the BRIDG program will train postdoctoral researchers who want to learn clinical research in a variety of CIH practices, including naturopathy, Chinese medicine, herbal medicine, nutrition, and mind-body therapies. The T90/UW program component will train postdoctoral CIH clinicians in a variety of clinical research methods.

NCNM thanks the NCCIH for generously supporting these two research training programs (Senders K23—1K23AT008211 and Zwickey R90—1R90AT008924). To learn more about the NCCIH training and development grants, visit https://nccih.nih.gov/training/about.

Visit NCNM's Helfgott Research Institute at www.helfgott.org to learn more about the BRIDG program or other research studies under way. Visit www.ncnm.edu/sorgs to learn more about NCNM's School of Research & Graduate Studies and its postgraduate degrees.

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Metagenics' 4th Annual Lifestyle Medicine Summit Prepares Health-Care Professionals to Preserve Patient Vitality through First 100 Years

Metagenics Inc., a nutrigenomics and lifestyle medicine company focused on improving health, will host its fourth annual Lifestyle Medicine Summit in Phoenix, Arizona, on September 25–27, 2015. The theme for the 2015 Lifestyle Medicine Summit is "Healthy Aging – 100% Vitality for Your First 100 years: Restoring and Maintaining Optimal Health." This landmark educational conference will convene leading health-care professionals and researchers who are transforming lifestyle medicine with cutting-edge insights and innovations to address the most critical health issues affecting the aging population.

"With an unprecedented increase of older adults living longer, forward-thinking strategies to protect and preserve their health and well-being are critical," said John Troup, PhD, chief science officer of Metagenics. "The Lifestyle Medicine Summit offers health-care practitioners across all specialties the opportunity to advance their knowledge in contemporary lifestyle medicine approaches to preserve patient vitality and help foster positive clinical outcomes for the aging population."

Venerated researchers and health-care professionals will share insights on how personalized diagnostics can be combined with smarter nutritional approaches and contemporary lifestyle medicine to make a difference in patient outcomes. Speakers and topics for this year's event include:

- **Jeffrey Bland, PhD, FACS, CN**: *Why the Solution to the Chronic Disease Epidemic is Personalized Lifestyle Health Care.*
  Founder and President, Personalized Lifestyle Medicine Institute; well-known functional medicine pioneer, research scientist, and educator; author of *The Disease Delusion.*
- **Charles Serhan, PhD**: *Novel Pro-Resolving Mediators in Resolution of Inflammation and Tissue Regeneration.*
  Director, Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital; professor, Harvard University; NIH Program Director/Principal Investigator, Resolution Mechanisms in Acute Inflammation: Resolution Pharmacology.
- **Fabrizio Mancini, DC**: *Aging Gracefully: 5 Steps to a Healthy You.*
  President Emeritus, Parker University; author of *The Power of Self-Healing* and *Four Steps for Living a Fabulous Life*; television health expert; host of the Hay House Radio show *Self-Healing.*
- **John E. Morley, MB, BCh**: *Achieving Vitality.*
  Professor of Gerontology and Director of Geriatric Medicine, St. Louis University Medical School; Director, Division of Geriatric Medicine; director, Division of Endocrinology at St. Louis University Medical Center; author of *The Science of Staying Young.*
- **Dale E. Bredesen, MD**: *Dawn of the Era of Treatable Alzheimer's Disease.*
  Director and Principal Investigator, Easton Center for Alzheimer's Disease Research at UCLA.
- **Dara Torres, Olympic Medalist**: *Healthy Aging in the 21st Century.*
  Twelve-time Olympic medalist; *New York Times* best-selling author of *Age is Just a Number: Achieve Your Dreams at Any Stage in Your Life*; correspondent, CBS Sports *We Need to Talk*

Other presenters and workshop leaders include Bridget Briggs, MD; Mimi Guarneri, MD; Robert Silverman, DC.; Ashley Howell, CHC; Maryam Kavousi, MD, PhD, FESC; Chris Keroack, MD; Robert Martindale, MD, PhD; Bob Rakowski, DC, CCN; Cory Rice, DO; and Charles Heroux, DC.

About the 2015 Lifestyle Medicine Summit

The Lifestyle Medicine Summit will be held at the JW Marriott Phoenix Desert Ridge Resort & Spa on September 25–27. For more details and registration information, please visit: www.metagenics.com/2015summit or call 800-692-9400 (US), 800-268-6200 (Canada).

Registration is $399. Early registration is recommended, as the Lifestyle Medicine Summit has sold out the past two years.

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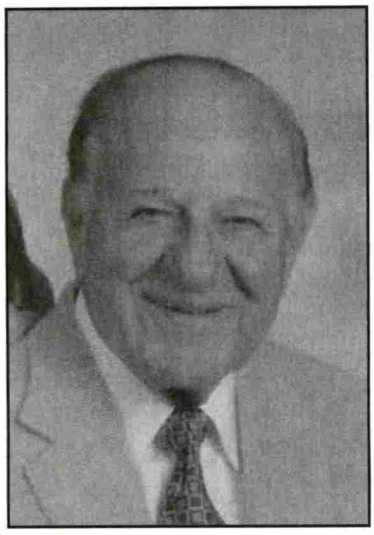

In Memoriam: Paul Parente, DO
1930–2015

Paul Parente, DO, passed away on 28 May 2015, after a long illness. He was known as an excellent integrative physician who always had time to teach and support his colleagues at the Great Lakes College of Medicine (now known as the International College of Integrative Medicine). He was a long-time board member and served as its president. He was an inspiration to the rest of us, especially showing us how his partnership with Dr. Al Scarchilli not only thrived but together they were so much more than either of them apart. Paul practiced in Farmington Hills, Michigan, for many years, which was a gift to the citizens of the Detroit area, and patients who came from Canada to see him as well. Our condolences to Barbara, children, and grandchildren.

Terry Chappell, MD

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Aneuploidy in Cancer

For over 30 years, researchers have sought mutated regulatory genes (oncogenes), believed to cause cancer. The failure to find any oncogene whose presence on its own initiates cancer has pushed some researchers to reconsider a 100-year-old theory, first proposed by German scientist Theodor Boveri: the aneuploid cancer theory. The aneuploid theory focuses on chromosomes instead of genes. Normal human cells have pairs of 23 standard chromosomes (a diploid karyotype). All cancer cells, however, have highly irregular chromosome patterns (aneuploid karyotypes): "entire chromosomes, which carry thousands of genes, are ... severely scrambled – duplicated, broken, structurally rearranged or missing entirely," says molecular biologist Peter Duesberg in a 2007 article for *Scientific American*.

A missing chromosome means that the genes it holds are also gone – genes that regulate the expression of important proteins. Conversely, extra copies of a chromosome means more copies of the genes and more of the corresponding polypeptides. "Such gross imbalances would inevitably disrupt the work of critical teams of enzymes, including those involved in repair or disposal of damaged DNA, and would destabilize cellular structures and regulatory circuits," Duesberg explains. Usually, cells that become aneuploid during mitosis do not survive. Those that do will propagate increasingly irregular cells, eventually forming a tumor. "Once cancer progression is underway, random chromosome reshuffling can rapidly generate gratuitous traits that include lethal properties such as drug resistance and metastasis," says Duesberg.

The aneuploid theory was tossed aside about 50 years ago because researchers were unable to detect any chromosomal patterns with available technology. New technology, however, lets researchers track chromosomal changes using colored DNA-specific probes. Research teams are finding chromosomal patterns in the same cancer types found in different people. Duesberg says that these patterns may reflect essential chromosome changes needed to create a viable aneuploid cell from the original normal tissue. Researchers are also finding chromosomal patterns associated with cancer stage, metastatic potential, and drug resistance.

All carcinogens cause aneuploidy, even though they may not cause genes to mutate. Asbestos, aromatic hydrocarbons, nickel, arsenic, lead, plastic and metallic prosthetic implants, and dioxin are among the carcinogens that disrupt chromosomes but do not cause gene mutation. Duesberg says, "The dose of carcinogen needed to initiate the process that forms malignant tumors years later was found to be less than one-thousandth the dose required to mutate any specific gene."

If the aneuploid theory proves correct, diagnosticians will be able to distinguish early cancers from benign tumors by looking for aneuploidy. They will also be able to use chromosomal patterns to determine cancer cells' metastatic potential and drug resistance. Moreover, regulators and manufacturers will be able to identify aneuploid-inducing substances *before* adding them to foods, drugs, and other consumer products.

Perhaps, cancer prevention can go even one step further and identify factors that decrease aneuploidy and encourage cells to remain diploid.

Duesberg P. Chromosomal chaos and cancer. *Sci Am.* May 2007;53–59. Available at www.davidrasnick.com/Cancer_files/Dues.Sci.Am.cancer.pdf. Accessed June 29, 2015.

Cancer Research

"Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas," say C. Glenn Begley and Lee M. Ellis in their 2012 commentary for *Nature*. They attribute the high failure rate primarily to the published preclinical research that forms the groundwork for drug development. Even at its best, preclinical cancer research focuses on a limited number of tumor cell lines that cannot reflect the complexity of cancer found in a human being. Too often, however, these limitations are superseded by an even greater problem: the results of many "landmark" preclinical studies, offering new treatment avenues, cannot be reproduced.

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Shorts

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When scientists at biotech firm Amgen's hematology and oncology department reexamined 53 studies related to a proposed line of new research, they were dismayed that only 6 (11%) could be reproduced – even after the original authors were contacted for directions. The 53 studies suggested new ways to use existing drugs or introduced novel treatment ideas. Amgen scientists expected some of them to fail but not the majority. Amgen is not the only company to encounter this problem. Bayer HealthCare (Germany) could reproduce the results of about 25% of the preclinical studies related to its own research and development projects. "In studies for which findings could be reproduced, authors had paid close attention to controls, reagents, investigator bias and describing the complete data set," say Begley and Ellis. "For results that could not be reproduced, however, data were not routinely analyzed by investigators blinded to the experimental versus control groups."

Good quality preclinical research needs to use the same precautions to avoid bias that well-designed clinical studies use. Preclinical studies should include positive and negative controls, and investigators need to be blinded. Begley and Ellis also recommend that key experiments be repeated by different investigators in the same lab whenever possible and that the final publication reflect all results.

"Journal editors, reviewers and grant-review committees often look for a scientific finding that is simple, clear and complete – a 'perfect' story," say Begley and Ellis. "It is therefore tempting for investigators to submit selected data sets for publication, or even to massage data to fit the underlying hypothesis." Journal editors, funding agencies, conference organizers, and reviewers need to value well-designed studies even if the results are inconclusive or negative. And readers need to check the quality of a study's design before being impressed by its groundbreaking discovery.

Begley CG, Ellis LM. Raise standards for preclinical cancer research. *Nature*. March 29, 2012; 482;531–534. Available at www.nature.com/nature/journal/v483/n7391/full/483531a.html. Accessed June 25, 2015.

Early Palliative Care

Palliative care is often considered end-of-life care, but recent studies are shifting the definition to "specialized medical care ... that focuses on relief from symptoms, pain, and psychological distress associated with serious illness," according to Lynn Howie and Jeffrey Peppercorn. Using palliative care early in the treatment of advanced cancer instead of waiting until death nears provides several benefits for patients, according to their 2013 review article. People with advanced cancer often experience pain, dyspnea, nausea, fatigue, and other symptoms that negatively affect mood and quality of life. Focusing on symptom management during the treatment stage improves patient satisfaction and reduces anxiety and depression. In addition, early palliative care initiates discussions about patients' goals and preferences so that the information can be incorporated into their care. Contrary to expectations, supplementing active treatment with palliative care appears to reduce overall health costs. Randomized studies have shown that patients receiving early palliative care have fewer emergency room visits and spend fewer days in the hospital.

In addition to improving quality of life and mood, early palliative care increased survival time in a 2010 randomized study led by Jennifer S. Temel, MD. The study randomly assigned 151 patients with newly diagnosed metastatic non-small-cell lung cancer to receive standard care or standard care with palliative care. All treatment was provided at a single medical center, Massachusetts General Hospital (Boston). "Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, $P=0.05$), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, $P=0.02$)," say the authors. The study did not have an attention control arm, which would have helped clarify that palliative care, rather than just additional caregiver time and attention, made the difference. Nonetheless, this study prompted the American Society of Clinical Oncology (ASCO) to issue a provisional clinical opinion advising that palliative care be given to newly diagnosed metastatic lung cancer patients.

Howie and Peppercorn point out that the Temel study cannot be generalized to other types of cancers. More research is needed to determine the most effective time to integrate palliative care for cancers with more variable survival times and to identify the components of palliative care that provide the most benefits. The delivery method for palliative care also needs to be investigated. The Temel study had the advantage of providing conventional care and palliative care at the same facility, which facilitated integration. Moreover, all studies in the Howie-Peppercorn review article used palliative care specialists.

Providing similar care in real-world clinical practice is hampered by the limited number of palliative specialists and by reimbursement systems that balk at paying for disease treatment and palliative care at the same time. Given these barriers, some have suggested that oncologists receive communication and symptom management training that enables them to provide early palliative care. "Oncologists with this training may have ongoing discussions with their patients from the diagnosis of metastatic disease which lead to less use of third- and fourth-line therapies which are less effective and may be more toxic, and may ease the transition from cancer-directed therapies to palliative therapies for their patients with advanced illness," say Howie and Peppercorn. Comparison studies could evaluate the different effects – if any – between receiving palliative care from a specialist and a trained oncologist.

Contrary to expectation, early palliative care that

continued on page 27 ➤

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includes realistic discussions about prognosis does not "reduce patient hope," say Howie and Peppercorn. Rather, it is an opportunity for patients to consider their goals and determine their care preferences before end of life. That opportunity can be empowering.

Howie L, Peppercorn J. Early palliative care in cancer treatment: rationale, evidence and clinical implications. *Ther Adv Med Oncol.* 2013;5(6):318–323. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3799294/pdf/10.117. Accessed June 24, 2015.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* August 19, 2010;363(8):733–742.

Intravenous Vitamin C and Cancer

People with cancer typically have *"very low vitamin C reserves,"* according to Ron Hunninghake, MD, so low that they develop scurvy. Hunninghake is chief medical officer at the Olive W. Garvey Center for Healing Arts, the clinical division of the Riordan Clinic in Wichita, Kansas. The molecular structure of vitamin C (ascorbic acid) is very similar to glucose, the primary fuel for cancer cells. Cancer cells actively absorb vitamin C, depleting the body's tissue reserves. Fatigue, listlessness, easy bruising, poor appetite, sleep disturbance, and low pain threshold – all of which are common among cancer patients – are also symptoms of scurvy. High-dose intravenous vitamin C (IVC) reduces pain, improves appetite and sleep, and helps cancer patients better tolerate chemotherapy and radiation treatment.

Intravenous administration of vitamin C is essential for effective treatment in cancer patients. Oral doses cannot raise plasma levels above ≈ 220 μM (micromolar), even with 3-gram doses given 6 times a day. At oral doses over 200 mg, vitamin C absorption decreases and urine excretion increases, according to a review article by Juan Du et al. However, plasma ascorbate reaches pharmacological levels when given intravenously. A 10-gram infusion of vitamin C produces plasma concentrations from 1 to 5 mM (millimolar). These pharmacologic levels have the additional benefit of selectively killing some cancer cells. "If large amounts of vitamin C are presented to cancer cells, large amounts will be absorbed," Hunninghake writes. At large concentrations, vitamin C interacts with copper and iron located in cancer cells and produces hydrogen peroxide. Eventually, the peroxide reaches a level that kills the cell.

Published clinical evidence that IVC can be an effective cancer treatment is sparse but not nonexistent. A 2006 article presents three case studies (using NCI Best Case Series guidelines) of patients with advanced cancers who received IVC therapy "as their only significant cancer therapy." A 51-year-old woman experienced complete regression of metastatic renal cancer after receiving IVC therapy (65 grams twice per week) for 10 months. (More than 4 years after treatment, she was diagnosed with small-cell lung carcinoma that did not respond to IVC.) A 49-year-old man with stage 2 (muscle invasive) bladder cancer had the tumor alone removed, leaving the bladder intact, and commenced IVC (30 grams, twice a week, for 3 months; then 30 grams once every 1–2 months for 4 years). Nine years after diagnosis, he was in good health. A 66-year-old woman with stage III diffuse large B-cell lymphoma agreed to 5 weeks of local radiation therapy along with IVC therapy (15 grams, twice per week for 2 months; once or twice a week for seven months; then once every 2–3 months for about a year). Ten years after diagnosis, she was in good health. Sebastian J. Padayatty and coauthors state, "Although they do not provide grounds for advocating intravenous vitamin C therapy as a cancer treatment, these cases increase the *clinical plausibility* of the notion that vitamin C administered intravenously might have effects on cancer under certain circumstances."

More recently, Jeanne Drisko, MD, and Qi Chen, PhD, have been conducting in-depth research on IVC use as a cancer treatment, according to an August/September 2014 *Townsend Letter* article (available online). Their small 2014 clinical study involving 27 women with advanced ovarian cancer indicated that high-dose IVC could reduce chemotherapy's toxic effects while increasing the treatment's effectiveness. The study also showed a trend of delayed cancer progression among women receiving IVC. Drisko and Chen are planning to conduct larger clinical population-based studies to track tumor response and clinical outcomes.

Although high-dose IVC is considered safe for most people, there are some contraindications. Some people with glucose-6-phosphate dehydrogenase deficiency have developed hemolytic anemia after receiving high doses of C. High-dose C may also increase iron absorption, making it unwise for people with systemic iron overload. High-dose IVC is not recommended for people with renal insufficiency or who are undergoing dialysis because ascorbic acid is metabolized to oxalate. Acute oxalate nephropathy has been reported.

For patients who can tolerate it, Hunninghake views IVC as a valuable adjunctive cancer treatment. He says, "IVC can help cancer patients withstand the effects of their traditional therapies, heal faster, be more resilient to infection, develop a better appetite, and remain more active overall. These things promote a better response to their cancer therapy."

Du J, Cullen JJ, Buettner GR. Ascorbic acid: Chemistry, biology and the treatment of cancer. *Biochim Biophys Acta.* 2012;1826:443-457. Available at www.ncbi.nlm.nih.gov/pubmed/22728050. Accessed June 24, 2015.

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Hunninghake R. Intravenous vitamin C and cancer [online article]. Orthomolecular.org. http://www.orthomolecular.org/library/ivccancerpt.shtml. Accessed June 24, 2015.

Padayatty SJ, Riordan HD, Hewitt SM, Katz A, Hoffer J, Levine M. Intravenously administered vitamin C as cancer therapy: three cases. *CMAJ.* March 28, 2006;174(7):937–942. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC1405876/pdf/20060328s00017p937.pdf. Accessed June 24, 2015.

Nigella Sativa (Black Cumin)

Nigella sativa (black cumin or black seed) is a spice revered for its medicinal properties by Ayurvedic, Chinese,

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and Unani (Arabian/Islamic) medicine practitioners. Although *Nigella sativa* is unfamiliar to most Westerners, Muslims consider it one of nature's greatest medicines. The seeds and their oil have been used traditionally for thousands of years to treat diarrhea, skin disorders, high blood pressure, liver disorders, infections, digestive complaints, diabetes, and cancers. Modern research indicates that the seed has antioxidant, anti-inflammatory, immunomodulatory, and analgesic properties among its pharmacological effects, according to a 2013 review article by Aftab Ahmad and colleagues. Thymoquinone (TQ) appears to be the main source of the seed's biological effects. It constitutes over one-third of the seed's active compounds. Thymoquinone has antioxidant, antimutagenic, and anticancer properties, according to in vitro and animal research.

Although *N. sativa* has a long traditional history as an anticancer treatment, modern research is just beginning. In vitro studies show that *N. sativa* extracts inhibit numerous cancer cell lines by inducing cell death in some and slowing proliferation in others, according to a 2011 review by Md. Asaduzzaman Khan et al. Animal studies indicate that *N. sativa* oil protects against cancer formation. Oral administration of *N. sativa* oil inhibited tumor formation in rats exposed to five different carcinogens, according to Ahmad et al. I was unable to find any human clinical studies at this time.

Toxicology studies indicate that oral use of *N. sativa* seeds, oil, and TQ is safe. The only caveat is that the botanical may affect the pharmacological effect of coadministered drugs. *N. sativa* extracts inhibit cDNA-expressed human cytochrome P-450-mediated metabolism.

Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Biomed.* 2013;3(5):337–352. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3642442/pdf. Accessed June 24, 2015.

Khan MA, Chen H-c, Tania M, Zhang D-Z. Anticancer activities of Nigella sativa (black cumin). *Afr J Tradit Complement Altern Med.* 2011;8(5):226–232. Available at www.ncbi.nlm.nih.gov/pubmed/22754079. Accessed June 24, 2015.

Radical Remissions

Oncology researchers estimate that 1 in 65,000 cancer patients experiences a spontaneous remission. Psychotherapist-researcher Kelly Turner, PhD, believes that this estimate is too low. Upon learning that no one was studying these anomalies, Turner decided to pursue a doctorate and do the research herself in the belief that these patients hold important clues about healing, specifically about healing from cancer. She visited 10 countries and interviewed 50 holistic healers and 20 radical remission cancer survivors for her dissertation. After obtaining her doctorate, Turner founded the Radical Remission Project to continue researching unexpected cancer remissions that occur after Western medicine has failed or without the use of any Western medicine. During an interview on May 21, 2015, Turner reported documenting 1000 cases of radical remission so far. She chose "radical" instead of "spontaneous" because "spontaneous" connotes a lack of effort or due to no external cause, a connotation that she finds inaccurate.

Although patient diagnoses differ, Turner has observed nine commonalities in those who experienced radical remission. She emphasizes that these factors are just preliminary observations, not conclusive causes or guarantees. Although their journeys to health varied in details, all of the patients took active control of their health and followed their intuition and hunches. "Radical remission survivors listen to the voices in their heads that whisper, 'Your job is killing you,' 'Move your body,' or, 'Look for other options,'" she writes. "These gut feelings come from the oldest parts of our brains – parts that we all have but rarely use, because we no longer need to predict hurricanes or know when a tiger is lurking." Many patients made dietary changes such as avoiding refined sugar and processed foods and increasing consumption of fresh, organic vegetables and fruits. Some patients found herbs and supplements helpful, even necessary for complete healing. Protocols vary, according to individual need.

To Turner's surprise, the remaining five factors were psychoemotional rather than physical. For some, releasing suppressed emotions was the primary change needed to recover their health. "Even happiness, when held onto, quickly turns into nostalgia for the past, as opposed to joy for the present," Turner writes. People who experienced radical remission also consciously fostered positive emotions each day – even for 5 minutes – by appreciating the sunrise, petting their cat, or engaging in other activities that brought a smile to their faces. They also welcomed the love and support offered by friends, family, and pets. A daily meditative or spiritual practice that produced a deep, peaceful rest and recharged their energy was another factor. The final commonality was having a strong purpose or reasons for living. Turner discusses these points in greater detail in her book *Radical Remission: Surviving Cancer Against All Odds.*

Turner says that ignoring these remission cases is "scientifically irresponsible." She believes that they can tell us a lot about the nature of healing.

Graedon J, Graedon T. Show 955: Surviving cancer against all odds – Dr. Kelly Turner, PhD [radio interview]]. *People's Pharmacy.* May 21, 2015.

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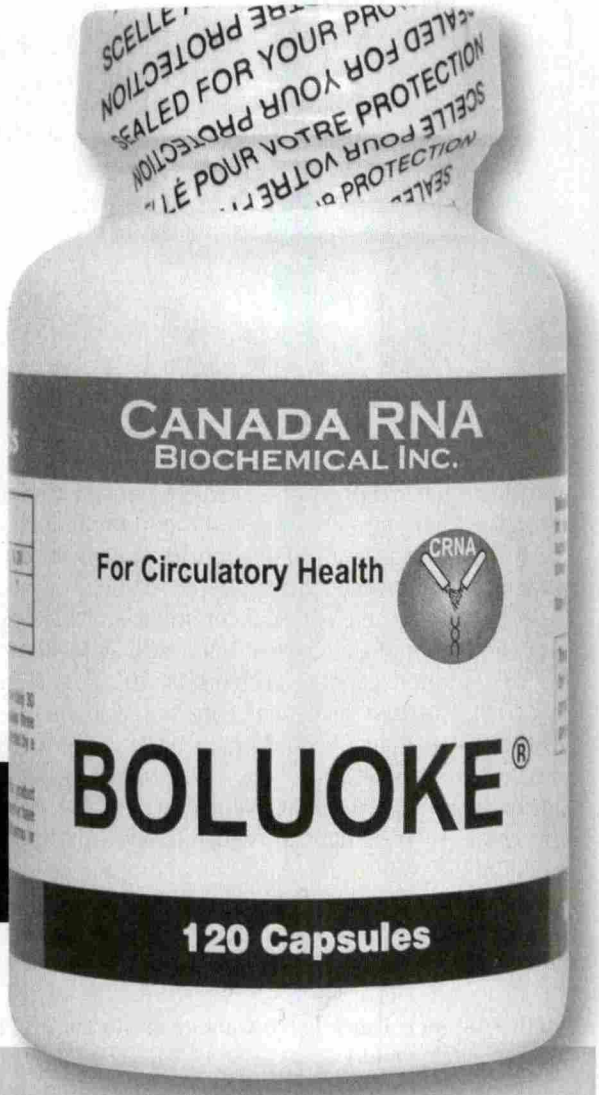

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Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Can the Environment Cause Cancer? Myth versus Fact

As cancer rates continue to climb, the focus for patients and doctors is on prevention. The American Cancer Society estimates that more than 1 million people in the US get cancer each year. Early detection, diagnosis, and treatments have greatly improved a person's outcome. Today 2 in every 3 people diagnosed with cancer survive at least 5 years. In fact, the National Cancer Institute (NCI) states that there will be 18.1 million cancer survivors in 2020, 30% more than in 2010. The cost of cancer care has also increased along with survival rates. According to NCI, in 2010 the cost of cancer care was $157 billion – yes, billion. Often times the unexpected expense that comes with a cancer diagnosis can create severe financial hardship. Prevention of cancer is the simplest way to decrease the cost of cancer. Cancer is a multifactorial disease with many possible causes. Genetics, lifestyle, and environmental factors have all been implicated. This column will explore the myths versus the facts.

Myth #1: Since There Is No Cancer in My Family, I Am Not at Risk

Only 5% to 10% of all cancer is caused by genetics inherited from a parent.[1] The rest is caused by something else. Genes can give us information on what our risk is for getting a certain disease, but genetics does not equal fate. Many other causes come into play, such as external factors – lifestyle and the environment – as well as internal factors – hormones and the immune system. A study conducted in Utah to determine the frequency of cancer in the first-degree relatives (parents + siblings + offspring) yielded interesting results. It provided an age-adjusted risk ratio to first-degree relatives of cases compared with the general population.[1] It determined that genetics played a role in only about 7% of cancers and the family risk ratio for certain cancers was as follows: Thyroid: 8.5; Testicular: 8; Laryngeal: 8; Multiple melanoma: 4.3; Lung: 2.6; Colorectal and kidney: both 2.5; Prostate: 2.2; Melanoma: 2.1; Breast: 1.8.

Genetic mutations have been discovered that are linked to an increased risk for a specific cancer. It is possible to test for these mutations. For example someone with the BRCA1 and/or BRCA2 gene has an increased risk for breast and ovarian cancer. The SCLC1 gene is linked with risk for lung cancer, and the CDKN2 gene is linked to malignant melanoma. When people know that they have a family history of a certain type of cancer, they may request genetic testing to help determine their risk factors. Some people with a strong family history *and* a genetic mutation undergo surgery to prevent cancer, such as Angelina Jolie's choice to remove both breasts and ovaries. This is a personal decision made between patient and doctor.

But simply having the genetic mutation doesn't guarantee that a person will get that cancer. For example, the concordance between identical twins for breast cancer was found to be only 20%.[2] Again, genetics doesn't equal fate. Genetic testing can provide useful information in trying to motivate someone to make lifestyle and environmental changes, especially knowing the genetic mutation often gets activated by an environmental factor. Since over 90% of cancers are due to something other than genetics, we must look at these other factors when discussing prevention of cancer.[1]

Myth #2: Exercise Can't Prevent Cancer

Exercise can lower the risk of developing certain types of cancer. This is an easy and inexpensive way to prevent cancer especially for people who have a family history or genetic mutation increasing their risk. Take colon cancer; as one example, a study that reviewed several observational trials found that moderate physical activity reduced colon cancer risk by 25% to 50%. One study showed that even just brisk walking 3 to 4 hours per week can lower colon cancer risk.[3]

There are numerous studies linking exercise to decreased risk of developing cancer. Some of the benefit may be in part due to body weight. People who exercise tend to maintain a normal body weight. Obesity is clearly linked to cancer. In fact, being overweight and inactive is known to increase the risk of breast, endometrial, kidney, colon, and esophageal cancer.[4]

Myth #3: Diet Has Nothing to Do with Cancer

Consumption of red meat is linked to an increased risk of colorectal, prostate, bladder, breast, gastric, pancreatic, and oral cancers.[5–12] Alcohol consumption, even 1 drink a day, is linked to several types of cancer, including breast cancer. Of course tobacco smoke is a known cancer-causing agent as well.[4] These external lifestyle factors linked to cancer are easily modifiable.

What is it about red meat that makes it carcinogenic? It has to do with chemicals, also known as environmental toxicants. The heterocyclic amines produced during the cooking of meat are carcinogens. Charcoal cooking or smoke curing of meat produces harmful carbon compounds such as pyrolysates, which have a strong cancerous effect. Nitrites and nitrates are used in meat and are powerful carcinogens.[4]

We are exposed to chemicals from other food sources as well. Bisphenol from plastic food containers can migrate into food and may increase the risk of breast and prostate cancers. Arsenic and mercury are present in rice and fish, and both are linked to cancer. This brings us to consider chemicals in the environment and cancer.

Myth #4: I Don't Work with Chemicals at My Job, So I Am Not at Risk

There is a clearly established link between occupational exposure to chemicals and cancer. According to the Agency for Toxic Substances and Disease Registry (ATSDR), being exposed to certain chemicals at work can cause specific cancers. This is considered high-dose exposure.[13]

However, nonoccupational or low-dose exposure to chemicals can also cause cancer. You don't have to work around chemicals to be exposed. Every day we come in contact with small amounts of chemicals in our air, water, food, and products. These chemicals are linked to cancer. For example, already mentioned above is the presence of cancer-causing chemicals in red meat. Another cancer-causing chemical produced when cooking meat is polycyclic aromatic hydrocarbons (PAHs).

PAHs: A number of studies show increased incidence of lung, skin, and urinary cancers when exposed to polycyclic aromatic hydrocarbons (PAHs). The primary source of PAHs is from burning carbon-containing compounds. PAHs in air are produced by burning wood and fuel for homes. They are also contained in gasoline and diesel exhaust, cola, cigar and cigarette smoke, and charcoal-broiled foods.[4] Foods that contain small amounts of PAHs include smoked, barbecued, or charcoal-broiled meats, roasted coffees, and sausages.

Cadmium: This is another chemical that we are exposed to daily in low doses through food, cigarette smoke, drinking water, and air. It is a known human carcinogen. Cadmium is introduced to the food chain through agricultural soils or from anthropogenic sources, from cadmium-plated utensils and galvanized equipment used in food processing and preparation, enamel and pottery glazes with cadmium-based pigments, and stabilizers used in plastics. The highest levels of cadmium in food are typically found in leafy vegetables such as lettuce and spinach, potatoes, grains, peanuts, and organ meats such as liver and kidney.[12] Cadmium is linked to lung, kidney, breast, and prostate cancer.[14]

Arsenic: Another cancer-causing metal, arsenic is found in small amounts in air, water, and food. Food is the largest source of exposure. According to the American Cancer Society, the highest levels of arsenic (in all forms) can be found in seafood, rice, rice cereal (and other rice products), mushrooms, and poultry, although many other foods can contain low levels of arsenic. It is linked to lung cancer via inhalation, as well as skin, stomach, and kidney cancer; leukemias; and lymphomas.[15]

Myth #5: The Air that I Breathe Can't Cause Cancer

Air: Many people believe that when they step outdoors to go for a walk, sit on the porch, or stand and talk to a neighbor, the air they breathe is safe. Since our federal and state governments regulate the outdoor air pollutants, it should be safe; unfortunately, this isn't the case everywhere. The International Agency for Research on Cancer (IARC),

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Cancers Associated with Various Occupations or Occupational Exposure	Substances or Processes
Lung	Arsenic, asbestos, cadmium, coke oven fumes, chromium compounds, coal gasification, nickel refining, foundry substances, radon, soot, tars, oils, silica
Bladder	Aluminum production, rubber industry, leather industry, 4-aminobiphenyl, benzidine
Nasal cavity and sinuses	Formaldehyde, isopropyl alcohol manufacture, mustard gas, nickel refining, leather dust, wood dust
Larynx	Asbestos, isopropyl alcohol, mustard gas
Pharynx	Formaldehyde, mustard gas
Mesothelioma	Asbestos
Lymphatic and hematopoietic	Benzene, ethylene oxide, herbicides, X-radiation system
Skin	Arsenic, coal tars, mineral oils, sunlight
Soft-tissue sarcoma	Chlorophenols, chlorophenoxyl herbicides
Liver	Arsenic, vinyl chloride
Lip	Sunlight

part of the World Health Organization, has listed outdoor air pollution as carcinogenic to humans. There are many individual compounds and mixtures in outdoor air that are known cancer-causing agents, but in 2013 the IARC took the bold step to list *air* as a cancer-causing agent.[16] Outdoor air pollution consists of several chemicals, including diesel engine exhaust, solvents, metals, and dust. It also contains particulate matter, as a carcinogen on its own. Particulate matter is a combination of extremely small solid particles and liquid droplets and can include elements such as dust or smoke, as well as chemicals. The biggest risk from air pollution is lung and bladder cancer.

Myth #6: My Food, Water Bottles, and Cosmetics Won't Hurt Me

Bisphenol A: BPA is a plasticizer found in baby bottles, hard plastic water bottles, the plastic lining of metal food cans, dental sealants, and the carbonless paper receipts that most cashiers hand out after a purchase at the store. It has been linked to breast cancer and prostate cancer in several studies.[17–22] BPA is being phased out voluntarily in some cases and by order in others. In 2012, the US Food and Drug Administration (FDA) banned the sale of baby bottles that contain BPA. However, it is being replaced by other bisphenols which are being found to have similar effects.[23]

Phthalates: These are a group of chemicals known as plasticizers and are found in cosmetics and personal care products, including perfume, hairspray, soap, shampoo, nail polish, and skin moisturizers. They are used in flexible plastic and vinyl toys, shower curtains, wallpaper, vinyl miniblinds, food packaging, and plastic wrap. Phthalates are also used in wood finishes, detergents, adhesives, plastic plumbing pipes, lubricants, medical tubing and fluid bags, solvents, insecticides, medical devices, building materials, and vinyl flooring. They are in literally hundreds of products, and we are exposed to them daily. Phthalates are linked to breast cancer.[24] The ATSDR lists phthalates as "Reasonably Anticipated to be a Human Carcinogen," meaning that it is just a matter of time.

Parabens: Parabens are among the most commonly used preservatives in cosmetic products. Chemically, parabens are esters of p-hydroxybenzoic acid. The most common parabens used in cosmetic products are methylparaben, propylparaben, and butylparaben. Cosmetics that may contain parabens include makeup, moisturizers, hair-care products, and shaving products. They are regulated by the FDA, which says that they are safe despite showing a link to breast cancer.[25] The FDA acknowledges the estrogenicity of parabens but states that low-dose exposure is safe. The FDA last updated its position on parabens in 2007.[26]

Myth #7: These Are the Only Environmental Links to Cancer

Obviously, this list is barely scratching the surface. People are exposed to many low doses of chemicals in the environment that are linked to cancer. Sometimes the exposure is enough to activate genetic predisposition for a specific cancer, turning on genetic mutation. This concept explains why some people exposed to low-dose chemicals get cancer and others don't. It is important for both doctors and patients to educate themselves about how to avoid environmental exposures to carcinogens.

Cancer is a multifactorial disease. Pinpointing a single cause is nearly impossible. Prevention really is the best medicine, especially in relation to cancer. It is important to identify genetic and heredity, lifestyle, and environmental factors. We can't change our genetics, but we can modify our lifestyle and minimize exposures to chemicals in order to decrease our risk of cancer.

Notes

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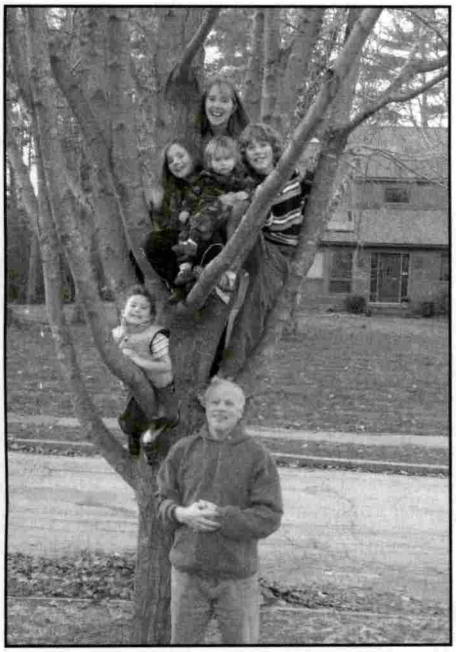

Literature Review & Commentary

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Beta-Carotene and Cancer: Not All Bad News

A prospective study nested within the Physicians' Health Study was conducted to determine whether supplementation with beta-carotene during radiation therapy for prostate cancer is associated with an increased risk of prostate cancer death or metastases. Three hundred eighty-three participants who had been randomly assigned to receive beta-carotene (50 mg every other day) or placebo underwent radiation therapy for prostate cancer while they were taking their assigned supplement. During a median follow-up period of 10.5 years, the incidence of the composite end point of prostate cancer death or bone metastases was nonsignificantly lower by 28% in the beta-carotene group than in the placebo group ($p = 0.24$). The 10-year freedom from the composite end point was 92% in the beta-carotene group and 89% in the placebo group.

Comment: Two previous double-blind trials have found that supplementation of cigarette smokers with beta-carotene increased the risk of developing lung cancer. In contrast, there is no evidence that beta-carotene increases cancer risk among nonsmokers.

Many oncologists are concerned about the possibility that beta-carotene or other antioxidants might interfere with the anticancer effects of chemotherapy or radiation therapy. As a result, cancer patients are frequently advised not to take nutrients such as selenium, vitamin C, or beta-carotene while they are receiving conventional cancer treatment. However, most research conducted to date has not found a deleterious effect of these nutrients, and in some studies the addition of antioxidants to chemotherapy or radiation therapy was associated with better outcomes. The results of the present study indicate that beta-carotene does not interfere with radiation therapy in men with prostate cancer, and may even increase survival and help prevent metastases.

Margalit DN et al. Beta-carotene antioxidant use during radiation therapy and prostate cancer outcome in the Physicians' Health Study. *Int J Radiat Oncol Biol Phys*. 2012;83:28–32.

Alpha-Linolenic Acid and Prostate Cancer

In the Alpha Omega Trial, 1622 patients (aged 60–80 years) who had a history of myocardial infarction and whose prostate-specific antigen (PSA) level was below 4 ng/ml were randomly assigned to receive, in double-blind fashion, 2 g per day of alpha-linolenic acid (ALA) or placebo in margarine for 40 months. The mean PSA level increased to a nonsignificantly greater extent with ALA than with placebo (0.52 vs. 0.42 ng/ml; $p = 0.12$). The probability that the PSA level would rise above 4 ng/ml was nonsignificantly higher by 15% in the ALA group than in the placebo group.

Comment: ALA is an essential fatty acid of the omega-3 class. It is present in high concentrations in flaxseed oil, canola oil, soybean oil, and some nuts, and in lesser amounts in a wide range of other plant and animal foods. Most, but not all, observational studies have found that higher intake of ALA is associated with an increased risk of developing prostate cancer. However, there is no clear evidence that ALA per se is responsible for this association. ALA at a physiological concentration has been reported to inhibit the enzyme 5-alpha-reductase in vitro. This enzyme catalyzes the conversion of testosterone to dihydrotestosterone, which is believed to play a role in the pathogenesis of prostate cancer. A substance that inhibits 5-alpha-reductase would be expected to prevent, rather than promote, prostate cancer. If the association between ALA intake and prostate cancer is causal, it may be due to the fact that ALA is a highly unsaturated molecule that is especially prone to becoming oxidized, either spontaneously or in the presence of heat. Most foods rich in ALA (e.g., cooking oils and roasted nuts) are heated before they are consumed. Heating ALA or oils high in ALA has been shown to produce a number of potential or probable carcinogens, including 1,3-butadiene, benzene, and acrolein. ➤

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In the present study, there was a trend toward an increase in PSA levels in men given ALA. However, the ALA-containing margarine used in the study was distributed only once every 12 weeks. It was not stated whether the tubs were airtight, or whether patients were advised to refrigerate after opening and to put the top back on immediately after use. Since ALA is unstable, it may have oxidized during storage, leading to the formation of potentially deleterious compounds.

The available evidence does not suggest that men should avoid foods such as raw nuts or non-rancid flaxseed oil in order to prevent prostate cancer. Many Western diets may already be marginally deficient in ALA, as a result of partial hydrogenation of edible oils and less grazing by farm animals on ALA-rich grasses. However, oils rich in ALA should not be used for high-temperature cooking. It would also seem preferable to consume nuts raw, as opposed to roasted. In addition, ALA-rich foods and oils should be refrigerated and stored in airtight containers, in order to prevent them from becoming rancid.

Brouwer IA et al. Effect of alpha linolenic acid supplementation on serum prostate specific antigen (PSA): results from the alpha omega trial. *PLoS One*. 2013;8:e81519.

Probiotic for Nonalcoholic Fatty Liver Disease

Forty-eight children (median age, 10.5 years) with biopsy-proven moderate or severe nonalcoholic fatty liver disease (NAFLD) were randomly assigned to receive, in double-blind fashion, the probiotic product VSL#3 or placebo for 4 months. The dosage was 1 sachet per day (450 billion organisms per sachet) for those aged less than 10 years, and 2 sachets per day for older children. The main outcome measure was the change in fatty liver severity at 4 months, as determined by ultrasonography. Compared with placebo, the probiotic significantly decreased the severity of NAFLD ($p < 0.001$). At the end of the study, the proportion of patients who had none or mild fatty liver was 91% in the VSL#3 group and 7% in the placebo group ($p < 0.001$).

Comment: NAFLD is a common condition among obese people and individuals with type 2 diabetes. It is characterized by fatty infiltration of hepatocytes. NAFLD appears to be an independent risk factor for cardiovascular disease, and in some cases it can progress to cirrhosis or hepatocellular carcinoma. Nutritional treatments that may be beneficial for this condition include weight loss if overweight, avoidance of dietary fructose, and supplementation with vitamin E and betaine. VSL#3 is a proprietary multistrain probiotic preparation that has been shown to be of value in the treatment of irritable bowel syndrome, inflammatory bowel disease, and minimal hepatic encephalopathy secondary to cirrhosis. The results of the present study demonstrate that this probiotic is also effective against NAFLD.

Alisi A et al. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2014;39:1276–1285.

Green Tea Extract for Xerostomia (Dry Mouth)

Sixty patients with xerostomia, including 10 with Sjögren's syndrome (7 in the active-treatment group, 3 in the placebo group) were randomly assigned to receive, in double-blind fashion, lozenges containing a proprietary preparation of green tea catechins (MighTeaFlow; Nomax Inc., St. Louis, MO) every 4 hours (maximum of 6 lozenges per day) or placebo for 8 weeks. All lozenges contained 500 mg of xylitol; the amount of green tea catechins in the lozenges was not stated. In the active-treatment group, compared with baseline, there was a significant 3.8-fold increase in unstimulated saliva output and a significant 2.1-fold increase in stimulated saliva output (stimulated by chewing neutral wax). Stimulated and unstimulated saliva output did not change significantly in the placebo group. No separate analysis was reported for the patients with Sjögren's syndrome. However, in a personal communication from one of the authors (Hsu S; December 10, 2014), in the subset of patients with Sjögren's syndrome, mean unstimulated saliva output increased significantly by 11.5-fold in the active-treatment group.

Comment: Xerostomia is dryness of the mouth resulting from insufficient saliva production. Consequences of xerostomia may include halitosis, impaired speech and taste sensation, altered dietary habits, and an increased incidence of dental caries (saliva contains factors that prevent caries). More than 400 medications can cause xerostomia, and medication use is the most common cause of this disorder. Other causes include Sjögren's syndrome and certain other autoimmune diseases, diabetes, mouth-breathing, excessive alcohol intake, nutritional deficiencies, and radiation therapy. Commercially available artificial saliva preparations are often prescribed, but no treatment has been shown to increase natural saliva production. This study provides new hope for people who suffer from dry mouth, including those with Sjögren's syndrome.

De Rossi SS et al. A phase II clinical trial of a natural formulation containing tea catechins for xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014;118:447-454.e3.

Iron Supplementation for Restless Legs Syndrome

Thirty patients (aged 20–80 years; mean age, 56 years) with restless legs syndrome and a low-normal serum ferritin level (15–50 ng/ml; suggestive of low or borderline-low iron status) were randomly assigned to receive ferrous sulfate (325 mg twice a day) or pramipexole (0.25 mg at bedtime, with the dosage adjusted at 2, 4, and 8 weeks according to response and tolerance) for 12 weeks. Symptom severity was assessed using the International Restless Legs Syndrome Study Group Rating Scale (IRLS) for severity. Treatment response was defined as a decrease in IRLS score of at least 50% from baseline. At baseline, IRLS scores and serum ferritin levels were similar between groups. Both groups improved significantly; the mean improvement was 41.6% with iron and 39.7% with pramipexole (difference between groups not significant). The response rate was 46.7% in each group.

Comment: Previous research has demonstrated that iron deficiency is a common cause of restless legs syndrome. Iron supplementation has been shown to be beneficial both in

patients with overt iron deficiency and in those with low-normal iron status. Pramipexole is a dopamine agonist that has been approved by the FDA for the treatment of restless legs syndrome. It can cause a wide range of side effects, including headache, edema, sedation, and abnormal movements. The results of the present study demonstrate that iron supplementation is as effective as pramiprexole in patients with restless legs syndrome and a low-normal serum ferritin level.

Lee CS et al. Comparison of the efficacies of oral iron and pramipexole for the treatment of restless legs syndrome patients with low serum ferritin. *Eur J Neurol*. 2014;21:260–266.

Fish Oil for Epilepsy

Twenty-four patients (aged 18–56 years) with drug-resistant epilepsy were randomly assigned to receive, in double-blind fashion, high-dose fish oil (3 capsules twice a day; 2,160 mg per day of eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]), low-dose fish oil (3 capsules per day; 1,080 mg per day of EPA + DHA), or placebo (corn oil) for 10 weeks. Each patient then received each of the other 2 treatments for 10 weeks, with a 6-week washout period between treatments. Compared with placebo, low-dose fish oil significantly decreased mean seizure frequency by 33.6% ($p = 0.02$) and high-dose fish oil nonsignificantly decreased seizure frequency by 3.7%.

Comment: Omega-3 fatty acids inhibit neuronal excitability and reduce seizures in animal models. High-dose fish oil has been studied in 2 randomized trials in patients with drug-resistant epilepsy, with negative results (Yuen AW et al. Omega-3 fatty acid supplementation in patients with chronic epilepsy: a randomized trial. *Epilepsy Behav*. 2005;7:253–258; Bromfield E et al. A randomized trial of polyunsaturated fatty acids for refractory epilepsy. *Epilepsy Behav*. 2008;12:187–190). The results of the present study suggest that the efficacy of fish oil is dose related: a lower dose (equivalent to about 3 g per day of fish oil) was effective, whereas a higher dose was not. In this study, the magnitude of the effect of low-dose fish oil was similar to that seen in recent clinical trials of antiepileptic drugs in patients with drug-resistant epilepsy. It is not clear why increasing the dose of fish oil might abolish its beneficial effect. However, there are other examples in nutritional medicine of a "therapeutic window," where both higher and lower doses are less effective than the optimal dose.

DeGiorgio CM et al. Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study. *J Neurol Neurosurg Psychiatry*. 2015;86:65–70.

N-Acetylcysteine for Methamphetamine Addiction

Thirty-two methamphetamine-dependent individuals seeking treatment were randomly assigned to receive, in double-blind fashion, 1200 mg per day of N-acetylcysteine (NAC) or placebo for 4 weeks. After a 3-day washout period, each person received the alternate treatment for an additional 4 weeks. Methamphetamine craving was assessed weekly, using the Cocaine Craving Questionnaire-Brief (CCQ-Brief). In the 23 subjects who completed the study, the mean CCQ-Brief score decreased (improved) progressively with NAC treatment. The mean scores in the NAC and placebo groups were 3.38 and 5.96, respectively, at the end of first session, and 4.57 and 3.2, respectively, at the end of the second session ($p < 0.001$ for the difference between NAC and placebo). Compared with placebo, NAC reduced methamphetamine craving by 43% in the first session and by 30% in the second session.

Comment: The presence of a subnormal concentration of glutamate in the nucleus accumbens region of the brain may increase compulsive or addictive behaviors and heighten cravings. Treatment with NAC has been shown to increase glutamate concentrations in the nucleus accumbens. In previous studies, NAC has shown potential as a treatment for cocaine addiction, nicotine addiction, and pathological gambling. The results of the present study suggest that NAC can also decrease methamphetamine craving. The lesser efficacy of NAC after the participants were crossed over to the alternate treatment may have been due to a carryover effect, since the score in the placebo group was lower in the second session than in the first session. That possibility is supported by a previous study, in which the beneficial effect of NAC in pathological gamblers persisted for 3 months after treatment was discontinued.

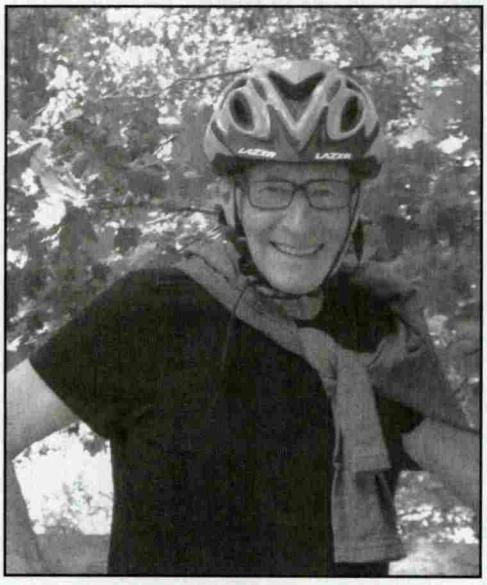
Mousavi SG et al. The efficacy of N-acetylcysteine in the treatment of methamphetamine dependence: a double-blind controlled, crossover study. *Arch Iran Med*. 2015;18:28–33.

Vitamin D: Could Toxicity Sneak Up on You?

Twenty-nine individuals (mean age, 62.5 years) with impaired glucose tolerance were randomly assigned to receive 20,000 IU of vitamin D3 or placebo once a week for 3 to 5 years. At the end of the treatment period, abdominal subcutaneous fat tissue was obtained by needle biopsy for measurement of vitamin D3 and 25-hydroxyvitamin D3 (25[OH]D) concentrations. In the group receiving vitamin D, median concentrations of serum 25(OH)D, fat-tissue vitamin D, and fat-tissue 25(OH)D were 99 nmol/L, 209 ng/g, and 3.8 ng/g, respectively. In the placebo group, these values were 62 nmol/L, 32 ng/g, and 2.5 ng/g, respectively. Assuming that an equal amount of vitamin D was stored in all adipose tissue in the body, the median body store in people given vitamin D supplements was 6.6 mg (264,000 IU) of vitamin D and 0.12 mg of 25(OH)D.

Comment: In this study, long-term supplementation with the equivalent of about 3000 IU of vitamin D per day increased serum 25(OH)D levels by 60%. In contrast, the mean concentration of vitamin D in fat tissue increased by 553%. The study did not investigate whether fat-tissue vitamin D levels plateau or continue to rise with continued supplementation. If the levels do continue to rise, vitamin D toxicity could develop after many years of supplementation with doses that are known to be safe in the short term. Vitamin D toxicity might be accompanied by an abrupt rise in the serum 25(OH)D level, but in the pretoxic phase, the serum 25(OH)D level might not accurately reflect the amount of vitamin D that has accumulated in the body. If toxicity does occur, it could take a long time to resolve, considering the large amount of vitamin D that has accumulated in fat tissue.

Didriksen AI et al. Vitamin D3 increases in abdominal subcutaneous fat tissue after supplementation with vitamin D3. *Eur J Endocrinol*. 2015;172:235–241. ◆



War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

Exciting New Tests for Cancer

This is an exciting time for noninvasive blood tests for cancer. Several biotech companies are vying to become the first to introduce a "liquid biopsy." This is a blood test that, as the name implies, can substitute for the often difficult, painful, and expensive surgical sampling of suspect tissues. Most of these blood tests are in development, but a select few are available now.

Janssen Diagnostics' test, CellSearch, has been available for several years. It was introduced by Viredex, a division of Johnson & Johnson. CellSearch cleared the Food and Drug Administration's approval process for circulating tumor cell (CTC) detection. It isolates the relatively rare somatic cell from billions of normal red blood cells. If a cell exhibits a number of stipulated markers, it is designated a cancer cell. An elevated number of such cells denotes a cancer of epithelial origin somewhere in the body, although the test does not differentiate among the many possible tissues of origin of the disease. The presence of CTCs in the peripheral blood is associated with decreased progression-free and overall survival in patients being treated for metastatic breast, colorectal, or prostate cancer. A 2007 study found that CellSearch has a sensitivity of 70% (Riethdorf 2007). In other words, 30% of those with advanced breast cancer show up as negative on this test. Janssen Diagnostics is also funding the work of Dr. Mehmet Toner of the Massachusetts General Hospital Center for Engineering in Medicine to create an even more accurate test.

Foundation Medicine of Cambridge, Massachusetts, is poised to become another big player in the cancer diagnostics field. Unlike most other start-ups, it is listed on the stock exchange, under the symbol FMI. The company provides two genome-based tests for patients, FoundationOne for solid tumors and FoundationOne Heme for hematologic malignancies and sarcomas. In a 2013 paper, the FoundationOne test identified base substitutions, short insertions and deletions, copy number alterations, and selected fusions across 287 cancer-related genes. The company reports a test sensitivity of between 95% and 99% (Frampton 2013).

ApoStream is a blood test from ApoCell, Houston, Texas. ApoStream analyzes differences in cell diameter, membrane area, density, conductivity, and volume to sort out tumor cells from normal peripheral blood mononuclear cells (PBMCs).

Other tests detect cancer-associated DNA or RNA. Guardant Health is offering its Guardant360 test. This is called "a targeted next-gen sequencing-based assay that assesses circulating tumor DNA." The company has received $10 million in funding from Sequoia Capital. The test looks for tumor DNA, which is shed into the bloodstream by nearly every type of cancer. Guardant360 requires two test tubes of blood. The company then sequences the genes and looks for genomic alterations that are typical of cancer. It is said to have a 90% sensitivity. The results are then reviewed by the company's Molecular Tumor Board and results are provided within 2 weeks of receipt of the sample. Guardant360 is available at select cancer centers in the US.

ENOX2 and ONCOblot

One or more of the above tests have a very good chance of making it to market. But, as fate would have it, the test that actually excites me the most may find it more difficult to gain widespread acceptance. Already this test is gravitating towards the complementary and alternative medicine (CAM) part of the market. This is ONCOblot, a test for the so-called ENOX2 (also called tNOX) protein. It comes from a relatively small company, MorNuCo Inc., based at the Purdue Research Park (West Lafayette, Indiana), headed by Profs. D. James Morré and Dorothy M. Morré.

Unlike most of the other tests, ONCOblot is a "tissue of origin" assay. This means that it can differentiate among 27 different types of cancer. This fact gives it the potential to become a reliable blood test, not just for tumors of known type, but also for cancers of unknown primary (CUP), one of the most difficult situations that confronts oncologists. ONCOblot can also tell whether or not a troublesome tissue abnormality is a metastasis or, perhaps, a second primary.

D. James and Dorothy Morré also have developed a dietary supplement, marketed independently of ONCOblot, which can reverse a positive score on this test in over 90% of cases (more on which in a moment). The companion treatment has enormous potential in the early treatment of undiagnosed early-stage cancers.

ONCOblot looks for variants of the ENOX2 protein (Tang 2007). ENOX 2 stands for ecto-NOX disulfide-thiol exchanger 2. The ENOX gene was independently confirmed by Colette M. Johnson et al. of the Hammersmith Hospital, London, in 2002.

What is ENOX?

The ENOX gene is located on the X chromosome. According to the Morrés, it is a tumor-specific member of the ECTO-NOX family of genes, which encode cell surface NADH oxidases. The encoded protein has two main activities: the first is NADH oxidation. This plays a role in cell enlargement and ultimately in cell growth. If this activity is unregulated, the developers say, it results in "the unregulated cell growth that defines all forms of cancer."

The second activity is to act as a terminal oxidase. Released energy is utilized to drive the enlargement phase of cell growth. In other words, this activity is a necessity for cells to increase in size. When this is inhibited, cells cannot divide and subsequently they undergo apoptosis (programmed cell death). Apoptosis is the common denominator of most successful chemotherapy. When ENOX2 is blocked, the cells divide once but are unable to divide again and subsequently undergo apoptosis.

Scientists at Hammersmith Hospital, London, have independently confirmed that ENOX (also called tNOX) plays an essential role in cell migration and cell survival (Su 2012).

Its downregulation, therefore, could be very important in preventing the spread of cancer.

According to the developers, the product of the ENOX2 gene is a cancer-specific universal cancer marker. In other words, the appearance of ENOX2 coincides with the onset of malignancy (uncontrolled invasive growth). The ENOX2 gene is not the result of a mutation, but is a part of the normal genome of vertebrate cells. It is normally only activated in the embryo. But in cancer, the embryonic gene is turned on once again. The gene product, ENOX2, is located at the cancer cell surface, whence it is readily shed into the blood circulation. According to the developers, ENOX2 protein is present in all forms of cancer thus far examined. It comes in a family of variants, in which each variant is specific to a particular tissue of origin. That is why the test can identify not only whether an individual has the beginnings of cancer, but which type of cancer has begun to grow in the body.

ONCOblot can often detect as few as 2 million cancer cells, which corresponds to a tumor as small as 0.8 mm in diameter. This is less than $^1/_{25}$ of an inch. One millimeter is also the thickness of a dime or the tip of a pencil. ONCOblot detects tumors smaller than that, which are unlikely to be found through conventional scanning. Positron emission tomography (PET) scans, for instance, can usually only detect tumors that are 10 times this size.

Although ONCOblot was designed primarily as a test for the tissue of origin of established tumors, people understandably want to know its sensitivity (i.e., rate of true positives) and specificity (i.e., rate of true negative). It appears to be higher in both regards than most approved tests. For example, the sensitivity of the prostate-specific antigen (PSA) test is just 21% for detecting any prostate cancer and 51% for detecting high-grade cancers (Meigs 1996). The sensitivity of colonoscopy is judged to be 95% (Rex 1997). Based on an analysis of almost 2000 cases, ONCOblot appears to be similar in sensitivity to this, although D. James Morré cautions that more evaluation is needed to more accurately establish the actual rates.

One of the great advantages of ONCOblot test for ENOX2 is that it is available now to medical doctors. (Consumers cannot apply on their own behalf, but the company also has a list of cooperative physicians.) The physician can order a test kit from ONCOblot Labs, fill out a requisition form, obtain a blood draw from the patient, and then follow the processing and mailing instructions included in the kit. The test can be used independently of any particular treatment plan, as it stands alone as a test for cancer.

There are presently 23 articles indexed in PubMed on the topic of ENOX2. Many (but not all) of these come from the aforementioned Purdue University laboratory and have the two main developers as coauthors.

One must be extra cautious in evaluating new cancer tests because the sums of money involved are so huge that it is possible for some individuals to exploit the pent-up demand for such a test. According to an article at the investment website seekingalpha.com: "The potential revenue from a test like this at a price of $500 could easily generate $10 billion in annual revenue just from the colon cancer screening market for a company that offers a liquid biopsy screening test" (Van Cuyk 2015).

When tens of billions of dollars are at stake, people can do funny things. In the Internet age, almost any person can make claims about the sensitivity of a test or the effectiveness of natural treatment and get away with it, for a while at least. Even a tiny fraction of this burgeoning market can make one a millionaire. So it is important to scrutinize all claims and proponents very carefully.

Two Outstanding Developers

One of the impressive things about ONCOblot is the history of the developers of this idea. They are, beyond doubt, well-qualified experts in their fields of study and have worked together for 40 years.

D. James Morré, PhD, is the Dow Distinguished Professor of Medicinal Chemistry (Emeritus) at the School of Pharmacy, Purdue University in West Lafayette, Indiana. Purdue is a public institution founded in 1869. Four of its professors have won the Nobel Prize, including Ei-ichi Negishi, another Distinguished Professor of Chemistry. Prof. Morré received his doctorate in biochemistry from the California Institute of

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Technology (Cal Tech), Pasadena, California, in 1963. He was the founding director of the Purdue Center for Cancer Research (1976–1986). In 2004, he received the Society of Sigma Xi Faculty Research Award (2004). He is the author or coauthor of more than 750 papers and reviews. He is listed among the 300 most-cited authors in science by Current Contents with 3065 citations for the 14-year period between 1965 and 1978. He also placed above the 95th percentile in the distribution of extramural NIH funds over the past 24 years, according to Columbia University.

His wife and coworker, Dorothy Morré, PhD, has had an equally distinguished career as a professor in Purdue's Department of Foods and Nutrition. She was a research scientist, Division of Membrane Biology and Biochemistry, Institute of Experimental Pathology, German Cancer Research Center, Heidelberg, Germany. She won the Gamma Sigma Delta Award for Outstanding Performance and Achievement in Research, Purdue University (2004). Dorothy Morré was a founding member, Botanical Center – Age-Related Disease, Purdue University. She is the author or coauthor of 170 publications. Dr. Morré was codiscoverer of the ENOX family of cell surface proteins and, together with her husband, coauthored the book *ECTO-NOX Proteins: Growth, Cancer, and Aging*, published by Springer, New York (2013).

Capsol-T

The other, equally exciting part of the ENOX story has to do with the Morrés' work on food supplements. Once they had the ENOX2 test in hand, they began to test various natural substances to see which would inhibit its activity. They found that the most effective such agent was green tea concentrate (better known as EGCG), which was potentiated by the addition of a small amount of capsicum (pepper). This was stimulated by work at the Institute of Biomedical Sciences, National Chung Hsing University, Taichung, Taiwan, which showed that capsaicin (from peppers) "induced cytotoxicity" in stomach cancer cells while down-regulating ENOX2 proteins (Wang 2008).

The Morrés' unique mixture is called Capsol-T. The first case treated with the mixture had an actinic keratosis (premalignant skin lesion), and was treated with a patch of an aqueous paste of these two botanicals. The primary tumor formed apoptotic blisters, whereas a second untreated carcinoma 17 centimeters distant also responded, which was indicative of a systemic action of the substance (Morré 2009). The combination of tea and pepper was far more effective than either alone (Forney 2013).

The most important article so far on the clinical effects of Capsol-T was published in *Clinical Proteomics* (Hanau 2014). This was a study of 110 subjects in the Lafayette, Indiana, area, ages 40 to 84, who were found to be positive for ENOX2 protein. They received 350 mg of Capsol-T in capsule form every 4 hours. This included during the night. They took this formula for at least 3 and as much as 6 months. After that time, they were again tested for ENOX2 using the ONCOblot Tissue of Origin Cancer Test protocol. Of the 110 subjects, with no evidence of clinical symptoms of cancer, 40% were positive for ENOX2 presence in the ONCOblot Tissue of Origin Cancer Test. The authors reported that "after completion of 3 to 17 months of Capsol-T use, 94 percent of subjects subsequently tested negative for ENOX2 presence."

A key characteristic of the treatment is that it *must* be given continuously every day. Patients therefore take 1 capsule every 4 hours. In order to facilitate a continuous period of sleep, the inventors also developed a sustained release (SR) form of their mixture (Janle 2008). The website for ordering Capsol-T is given at the end of this column.

These are amazing results. If this research can be generally confirmed, it will make a major dent in the cancer problem. One could foresee the day when the population could be screened for early-stage cancer using the ENOX2 assay, and those who test positive would undergo further diagnostic testing (to pinpoint the exact location of the tumor) and/or would be put on a regimen of Capsol-T to eliminate the early growth. This, at least, is the hope. Obviously, further validation will be necessary before this can come to pass. More research and trials are in the works, and I hope to write about these as they appear.

At the present time, the test is Clinical Laboratory Improvement Amendments (CLIA) approved and College of American Pathologists (CAP) accredited, and meets FDA requirements for a Laboratory Developed Test (LDT). However, it is not yet covered by most health insurance plans. The cost of each ENOX2 test is $850. Capsol-T costs about $1 per capsule (or $6 per day) and must be taken for 3 to 6 months. Total supplement cost is thus between $650 and $1300 per patient. Add in before and after tests and the total cost of diagnosis and treatment is between $2500 and $3000. This is a fraction of the typical cost of diagnosing and treating cancer, wherein new cancer drugs typically run to over $100,000 per patient. But since it is presently not covered by most insurance, this could be burdensome to many individuals.

Each dose comes in a clear, oval-shaped 350 mg "size 0" gel capsule. The capsules contained food-grade decaffeinated green tea powder and food-grade red pepper powder in a ratio of 25:1. Each dose is equal to 16 cups of green tea per day. A daily dose of caffeine is thus less than 10% of the caffeine of a single cup of coffee. The pepper used in the formula is guajillo, a relatively mild pepper, similar to bell peppers. It contains virtually no capsaicin, the "hot" element in most peppers.

Some people reading this may have advanced, recurrent, or well-established tumors. Could they take advantage of this test and treatment? There might be situations in which ONCOblot would be helpful. For instance, it could be used to identify a tumor of uncertain origin or to see whether a tumor has recurred. As to the green tea and pepper mixture, there are few published data concerning its effect on established tumors. But there is a wealth of information on the preventative effects of these food supplements

(Morré 1995; Morré 2009). There are presently over 2000 PubMed-indexed articles on green tea and cancer alone, with new articles appearing at a rate of 125 per year. Since the "side effects" of decaffeinated green tea are minimal to nonexistent, I see little reason other than price constraints not to try it.

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Resources

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.

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Probiotics vs. Heavy Metals: A Win for the Good Guys

by Bob Frost

Probiotics may be helpful in humanity's fight against heavy metals such as mercury and arsenic.

In a groundbreaking study, Dr. Gregor Reid and his team in Canada used probiotic-enriched yogurt to protect people against absorption of mercury and arsenic from the gastrointestinal tract into the bloodstream.[1]

According to Reid's study, yogurt infused with *Lactobacillus rhamnosus* GR-1 protected pregnant women against absorption of mercury by up to 36% and of arsenic by up to 78%. This is the first demonstration in humans of the theory that probiotic microbes can remediate environmental toxins in the gut, according to Reid. His paper was published in *mBio* (September/October 2014), a journal of the American Society for Microbiology.

Reid says the protective process used by probiotic microbes may be "passive sequestration" whereby the microbes bind to heavy metals in the gut and usher the metals harmlessly out of the body in the stool. By contrast, if heavy metals enter the bloodstream, they can make their way into organs such as the brain, heart, and liver, and do damage.

Reid is a professor of microbiology and immunology and surgery at the University of Western Ontario and also holds an endowed chair in human microbiome and probiotics research at Lawson Health Research Institute. Both institutions are in London, Ontario.

Reid's work is "pioneering" and "fantastic," comments Dr. Benoit Foligne of the Pasteur Institute of Lille, France: "This study confirms, at the clinical level, the promising use against toxins of selected probiotic strains – whether as supplements or as yogurt."

A robust new field is opening up, according to Foligne and Reid – deciphering the mechanisms of probiotics against toxins.[2]

Dr. Liz Lipski of the Maryland University of Integrative Health, author of *Digestive Wellness* (2012 4th ed.), comments, "Although the Reid project was a small pilot study of short duration, it opens the door for more research. Using probiotic-rich foods, and supplements, may be a safe and gentle way to prevent absorption of common heavy metals and enhance heavy metal detoxification."

Reid and his team studied 60 pregnant women and 44 children in Mwanza, Tanzania, in the northern part of the African country near Lake Victoria. Many people in the region carry substantial bodily loads of heavy metals, partly because of their diet.[3–5] They eat large numbers of silver cyprinid fish, laden with mercury, probably from gold mining in the region, which spews mercury into fish habitat. Mwanzans may also ingest heavy metals from air pollution, says Reid.

Many Mwanzans use mercury to help them find little fragments of gold in streams and rivers (as do millions of people around the world). The mercury binds with gold via a concentration process known as amalgamation. The website www.mercurywatch.org estimates that hundreds of tons of mercury are used annually by small-scale gold prospectors. Minuscule amounts of the metal, just a few grams, can be toxic over wide areas, notes Reid.[5]

Mwanzan children participating in the Reid study received a daily 9 oz serving of fresh, locally made yogurt, for 25 days. Each serving contained 10 billion colony-forming units of *Lactobacillus rhamnosus* GR-1. Children in control groups received either whole milk or no intervention. Pregnant women in the study received either daily yogurt for up to 3 months or no yogurt supplement.

Each yogurt serving cost only pennies. "The economics of this approach are promising," Reid says. "I would like to see people around the world empowered to make their own probiotic food – that's totally feasible if we give them access to the probiotic and starter organisms." Refrigeration, he says, need not be an issue. "People can buy milk straight from local farmers, make yogurt themselves, and eat it within days. It's an idea that can transform communities and countries."

He adds, "Humanity is not doing much to reduce mercury, arsenic, and other polluting chemicals, especially in the developing world. We have to do *something* to combat

these toxic compounds. Probiotic therapy appears to be a helpful tactic. Yogurt is inexpensive and is widely accepted."

Heavy metals and metalloids – mercury, arsenic, lead, cadmium, selenium, nickel, copper, etc. – can be toxic or poisonous at relatively low dosages or intakes. The materials have been associated by scientists with many diseases.[5–8] They can enter the human body via food, water, air, supplements, vaccines, and dental work. They're dangerous because they tend to bioaccumulate – over time, their concentrations increase in biological organisms.

The US government seeks limits on mercury pollution, but legislation is tied up in the courts.[9] Globally, the United Nations is spearheading an antimercury treaty, the Minamata Convention on Mercury, which will come into force when 50 countries have ratified it. So far, about a dozen nations have done this, including the US. Ratification is complex – it means "updating country laws on mercury pollution," says Dr. Joseph DiGangi, a science advisor for the antipollution network IPEN. Critics have blasted the Minamata pact as too weak.

One of the interesting sidelights of the Reid study concerns the silver cyprinid fish widely consumed by Mwanzans. These fish are 2 to 3 inches long. According to many studies, *large* fish (swordfish, etc.) have a higher concentration of mercury than small ones due to biomagnification.[10]

Reid and his team were surprised at the level of mercury and arsenic in the small fish of Lake Victoria and are "greatly concerned" about this. Reid comments, "Health practitioners recommend that people – especially pregnant women – avoid large fish because of mercury levels. Our finding about the level of mercury in small fish challenges this recommendation and indicates that it may need to be revised."

Reid, 59, has been a leader in probiotics research since the early 1980s – "since before probiotics were called that," he says. He is the cocreator of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14. He has been awarded 28 patents, has published more than 450 peer-reviewed papers, and has delivered 550 presentations to audiences in 53 countries. He served in 2001 as chair of a United Nations/World Health Organization expert panel on probiotics, and was president between 2006 and 2009 of the International Scientific Association for Probiotics and Prebiotics (ISAPP). He remains active today in the ISAPP. He got the idea for the Tanzania study in 2009 and received a grant for the project in 2012 from the Bill and Melinda Gates Foundation.

Reid was born in Barrhead, Scotland, near Glasgow. He had a difficult upbringing. When he was 12 years old, the UK government consolidated educational districts, and he found himself attending class with switchblade-wielding gang members – hooligans, as they were called in Scotland, also known as "neds." Reid was a well-mannered young scholar and was viciously bullied for years. He survived by listening to his parents: "Study," they said. "Work hard."

After high school, he wanted to pursue a career in medicine, but the University of Glasgow School of Medicine declined his application in 1974. He heard later that a number of his peers, with less impressive grades, gained acceptance to the school ahead of him because of their family connections.

His voice tightens as he recalls the unfairness of the admittance system and the bullying of his early years. He seems to have a very strong sense of justice and injustice. "Quite true," he says, "social justice is something I feel strongly about. Justice for people who are treated unfairly, whether by a college, peers, or a big corporation." He endorses the idea of "social business," a concept created by Nobel laureate Muhammad Yunus, who describes it as a "new kind of capitalism that serves humanity's most pressing needs."

Reid earned a microbiology degree with honors in 1978 at the University of Glasgow. At the suggestion of an American friend, he visited Michigan. Life felt different there, he says: "It seemed like opportunity was everywhere." His ambition soared. He won a Rotary International Graduate Scholarship, went to New Zealand for a PhD in microbiology, and did postdoctoral work at the University of Toronto, where, in the early 1980s, he formed a professional alliance with Andrew Bruce, MD, a major figure in the early history of probiotics research.

"Andrew and I were pioneers in probiotics," Reid says. "Some people have forgotten that. It's strange – in science, everyone likes to think that their brilliant idea comes entirely from their brain, from their lab. They forget about the deep sources for their idea" – the historical roots.

"People laughed at us," Reid recalls of his early work with Bruce. "Grant agencies rejected our ideas. We were undaunted!"

Reid says that he and Bruce were the first researchers to "truly target" probiotics for women's health.[11]

Probiotic milk was sold in Japan in the 1930s but had no apparent impact in the West. Drs. Barry Goldin and Sherwood Gorbach isolated and commercialized *Lactobacillus* GG (LGG) with Valio of Finland in 1987. This, says Reid, came "after our team began making breakthroughs." He says, "We were not comfortable commercializing a probiotic without knowing its properties, understanding its effects on humans, and showing it could benefit women. These things took many years."[12]

Reid says he has fought uphill battles for more than 30 years, urging conventional medicine to embrace probiotics, and advocating reform of governmental regulatory agencies such as the US Food and Drug Administration and Health Canada. He is "rather angry, actually" at the lack of change in "outdated" regulatory systems "designed for potent chemicals but not equipped to ➤

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deal with bacteria that are part of the human body."

At the same time, he is heartened by the bright-eyed enthusiasm of young people who are getting interested in probiotics. In the last 5 years, he says, the field has gotten "trendy." He gives a lecture about probiotics and the microbiome to second-year microbiology students: "They get totally excited! They envisage so many places where this field could go!"

On a scale of 1 to 10, with 10 being maximum positive impact on human health, Reid rates the impact of probiotics at "8." He explains: "I think beneficial microbes score a '10' – they represent the wider field, inclusive of probiotics. Fecal transplant is an example of using these organisms in a way that is not, strictly speaking, probiotic."

Every day at lunchtime, Reid eats a cup of yogurt. He also takes a daily dose of a product sold in Canada as RepHresh Pro-B, available in the US as Fem-Dophilus – "marketed for women's health," he notes, "but good for anyone's gut."

Next up for Reid and his team: helping people at the poor end of societies gain access to probiotic food, and integrating probiotic concepts into the care of patients who are hospitalized or chronically ill. He predicts, "Over the next 10 years we will see clear proof of the massive impact of beneficial microbes on people's well-being."

Among the key members of the Reid team for the Tanzania study were informaticist Dr. Jeremy P. Burton and microbiome expert Dr. Gregory B. Gloor. Reid's chair at Lawson is endowed with a $6 million contribution by the Dannon Company.

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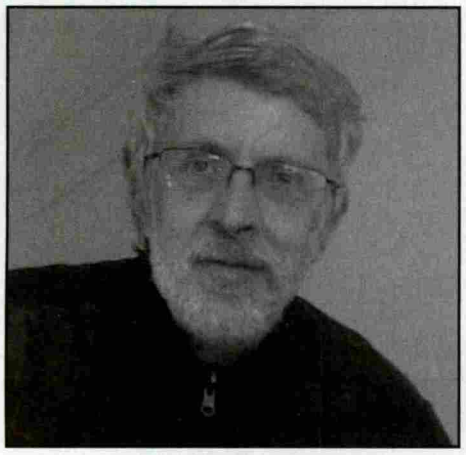

Bob Frost is a journalist in San Francisco specializing in coverage of health topics. He wrote about health care for many years for *West*, the Sunday magazine of the *San Jose Mercury News*, newspaper of record for Silicon Valley, including cover stories about pain, allergies, and the Great Influenza Pandemic of 1918. His e-mail address is bobfrostmail@aol.com.

Restoring Immune Function[1]: Nontoxic Cancer Therapy Utilizing Dendritic Cells

Robert Gorter, MD, PhD, and Erik Peper, PhD

Dendritic cell therapy has no side effects for me, except for a touch of flu, which means that the treatment is catching on. It does cause a temporary fever, which usually starts about an hour after the injection. Over the course of eight hours, the fever rises a little, in my case to about 102 F (39.5 C).

Somehow it feels fine – I feel as though something positive is happening. I don't feel ill. Although it's a real fever, somehow my body knows that I need this. And the results are fantastic. My MRI scans over the past five years have confirmed that the treatment has been successful.

Harmen Wagenmakers, five-year survivor of stage IV liver cancer (cholangiocarcinoma)

All healthy individuals continuously produce autologous cancer cells throughout their lives. Malignant cells result from the effects of mutations, viruses, and exposure to carcinogens ranging from radiation and tobacco smoke to pesticides and food additives, to mention a few.

Combating Cancer

In any human being, cancer cells develop by the thousands every day. As long as the immune system can detect and contain the flow of newly emerging malignant cells, one can go through life without ever having clinically developed cancer. When cancer occurs, by definition the immune response is suppressed, or there has been excessive exposure to carcinogenic substances. Impaired immune function often involves a drop in the number of highly specialized monocytes that detect cancer – the dendritic cells – or due to an impairment in their function.

Dendritic cells are antigen presenting cells that display the digested fragments of phagocytosed pathogens to other immune cells. Under normal conditions, dendritic cells migrate throughout the tissues of the body, checking for abnormal or malignant tissue. When an abnormal cell is detected, the dendritic cell travels to a nearby lymph node, presenting the antigen profile of the abnormal cell to natural killer cells and other cytotoxic T-cells. If the immune system is no longer able to recognize cancer cells, it cannot destroy them as they develop. When that occurs, cancer can gain a foothold and grow unchecked. Tumors can develop, amass, and remain undetected for years, as subclinical cancer.

Researchers have shown that fresh dendritic cells can be introduced into the body in the form of a vaccine. If cancer is present, inoculation with new dendritic cells alerts the immune system to the presence of cancer and restarts immune function. This serves to mobilize the exceptional power of the immune system to recognize cancer and combat it.

Development of Dendritic Cell Vaccinations

Dendritic cells are cultured from the patient's own white blood cells. After a simple blood draw, the blood is sent to a medical laboratory where technicians separate out monocytes from the blood. These cells are then cultured and transformed in seven days into a new generation of dendritic cells. This new generation of vital, activated dendritic cells is re-introduced into the patient's own body through a simple injection.

During the transformation of monocytes to dendritic cells in the laboratory, it is possible to specifically sensitize those cells to the patient's cancer if tumor tissue is available. When tumor tissue can be preserved following the patient's surgery, it is possible to isolate specific tumor antigens directly from that tissue. Dendritic cells are then exposed to the tumor-specific antigens, and are imprinted with these antigens before being reintroduced back into the body. This process of educating the dendritic cells is described as loading the dendritic cells.

After I had lung surgery to remove some additional tumors, we brought the material from the second lung to Cologne, because it contained active tumor cells. That tissue was used to make the dendritic cells.

Wim Koosterboer, survivor of hepatitis B and associated primary liver cancer with lung metastasis

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Nontoxic Cancer Therapy Utilizing Dendritic Cells

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In most cases, the protocol is applied with dendritic cells cultured from the patient's blood without loading them with tumor-specific antigens. Approximately 99% of all patients at the Medical Center are vaccinated with "naïve" dendritic cells. Yet the results are still remarkable by any standard, increasing immune response, patient survival, and quality of life.

Treatment History

Over the past 10 years, the Medical Center Cologne has treated roughly 3,800 of patients with dendritic cell therapy for conditions that included brain tumors, primary bone cancer and bone metastasis, breast cancer, colon cancer, liver metastasis of all kinds, cholangiocarcinomas, lung cancer, malignant melanoma, and prostate cancer. Using this protocol, patients with end-stage cancer frequently experience partial remission and stabilize for several years with highly positive quality of life. Some also experience complete remission. For example, 44% of all patients with *Glioblastoma multiforme* stage IV have experienced complete, long-lasting remission.[2] This is remarkable, given that the medical literature indicates approximately 95% of all patients diagnosed with *Glioblastoma multiforme* stage IV die within the first year of diagnosis.

These outcomes reflect the positive survival rates frequently seen in patients at the Medical Center Cologne. Dendritic cell therapy has been an integral aspect of cancer treatment there for more than 10 years, employing safe, effective protocols that have been replicated and repeatedly validated in the peer-reviewed literature. Today, research centers worldwide are studying dendritic cell therapy, and this treatment is rapidly gaining interest as a valid approach to cancer intervention.

Safety and Effectiveness

Dendritic cell therapy is widely recognized in the research literature as safe, with minimal toxicity at the lowest level (Grade 1). This nontoxic treatment is appropriate even for immune-compromised patients and those unable to detoxify medications. The injections are generally well tolerated with almost no side effects except for a 4- to 24-hour fever that typically starts the first day of the injection. Temporary side effects documented by Japanese researchers were "fever (78%), chills (83%), fatigue (23%), and some nausea (17%) experienced on the day of the cell [injections]."[3]

In my case, the dendritic cell therapy's symptoms were minimal and lasted no more than two days. The hyperthermia was uncomfortable for me personally, but it only took three hours. There were no side effects from the treatment. After that I felt better and could do what I wanted. The treatment did not exhaust me and because I was not exhausted, it was much easier to stay optimistic.

Harmen Wagenmakers, long-time survivor of stage IV liver cancer (cholangiocarcinoma)

Researchers have also pointed out that dendritic cell therapy offers a safe, effective, non-toxic treatment option for children.[4,5] Preliminary studies show that the vaccines are even more effective in younger patients than in adults.

Training the Immune System

When vaccinating for diseases such as tetanus or measles, the same injection must be repeated five to six times at defined intervals, in order to establish life-long immunity. To improve immune function using dendritic cells, cancer patients are initially vaccinated with dendritic cells six times at monthly intervals. Thereafter, the injections are repeated once every six months for the duration of three years as booster shots and then at annual intervals. The importance of frequent vaccination in the initial stage of treatment has been validated in scores of recent research studies.

The Gorter Protocol

In the Gorter Model, the first step in treatment is induced fever-range, total-body hyperthermia, or localized hyperthermia. Fever causes an immune response that is essential in eliminating the disease. We know that fever also serves to initiate tissue repair. This is well-documented in situations such as an accident or other types of events causing organ damage. It has also been demonstrated in numerous studies that fever induces the immune response at approximately 102°F (39.5 °C). The immune system then shifts into a highly activated state, in preparation for a system-wide attack on *any* deviant cells found. Broadly focused immune defenses such as NK cells are also called up. In short, fever primes the body for a full-force immune response. The second step in the protocol is the dendritic cell vaccination itself, which provides the means to identify the cancer cells as the target that must be eliminated.

In terms of dendritic cell therapy, I had the first six treatments in four weeks. I would receive the injection

and then after an hour and a half, I would start getting a fever. Before I got home, I would have a fairly high fever. It wasn't unpleasant – it never made me feel weak, whereas normally a fever might wear me down. Once I laid down and closed my eyes, I always fell asleep fairly quickly.

When I wake up the next day or so, it has already subsided a bit. I always develop a mild headache, but I don't take anything because the headaches are bearable. I rest that day, go for a walk, get some fresh air, and in the evening it's gone. That's it. Those are the only side effects I've ever experienced from the treatment.

Karl-Heinz Hagemeyer, four-year survivor,
stage IIIb metastatic prostate cancer

Dendritic Cell Research

Research studies confirm the effectiveness of this approach to immunotherapy. Study after study has shown that dendritic cell therapy provides anti-tumor effects and significantly prolonged survival. American studies of dendritic cell therapy have been conducted at major universities that include Harvard Medical School, UCSF Medical School, Stanford, University of Maryland, University of Michigan, and University of Texas.

There is broad agreement that dendritic cell therapy increases the number of T-cells, which results in a stronger immune response. Italian researchers reported, "Dendritic cell targeting...has recently been shown to confer strong and protective cytotoxic T cell-based immunity."[6] Studies at research centers around the world have documented the benefits of this therapy for many forms of cancer, including lymphoma, melanoma, metastatic kidney cancer, renal carcinoma, and thyroid cancer. In the U.S., in 2009, a controlled phase II study of metastatic prostate cancer demonstrated that dendritic cell vaccinations are an effective therapy.[7]

Long-Term Survival

Dendritic cell therapy improves the outcome of cancer treatment and frequently extends life for cancer patients by several years, with improved quality of life:

- In an Austrian study of 10 patients with metastatic thyroid cancer, 30% had stable conditions at one year.[8]
- Research conducted in Korea with 9 renal cancer patients found that 6 of 9 benefited from the dendritic cell vaccine, with an average survival of 2 ½ years.[9]
- German cancer research on metastatic thyroid conditions found that 5 of 10 patients survived more than 3 years with dendritic cell therapy.[10]
- A recent French study involving 56 cancer patients reported patient survival averaging almost 4 years.[11]
- An Italian study following the progress of relapsed lymphoma patients who were then treated with dendritic cell therapy reported that almost 80% were stable after 4 years.[12]
- Japanese research documented the health of 28 lung cancer patients and found a 2-year survival rate of 90% and 5-year survival greater than 50%.[13]

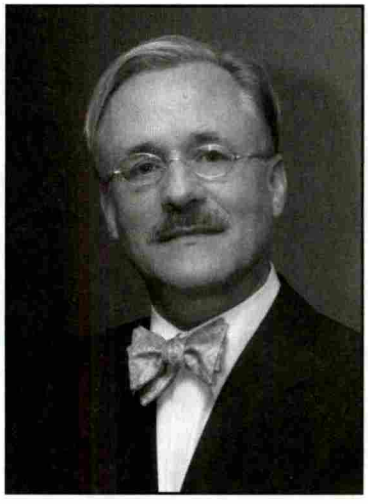
In a Chilean study of 50 patients, those with stage III cancer treated with dendritic cell therapy survived an average of 4 years. Among those with stage IV cancer, 60% responded positively to the treatment and lived almost 3 years.[14] This is an exceptionally positive result, since survival of stage 4 patients is usually measured in weeks or months. All of these studies involved some form of dendritic cell vaccine.

A Danish study found that one dendritic cell inoculation can double the number of T cells and NK cells in the body in as little as 4 weeks following the injection.[15] According to British researchers at the U.K. Institute for Cancer Studies, "Dendritic cells are the most potent of all antigen-presenting cells, with the capacity to take up, process, and present tumor antigens to T cells and stimulate an immune response, thus providing a rational platform for vaccine development."[16]

This non-toxic immune therapy offers an important option in cancer treatment. Dendritic cell vaccines provide another form of therapy for conditions that cannot be addressed with chemotherapy or radiation, such as metastatic renal cancer or malignant melanoma. The vaccine can be a life-prolonging therapy for stage III and IV patients and, for the vast majority of patients, enhances quality of life.

After I received the dendritic therapy, I recovered quickly and the next scans confirmed that all the cancer was gone. All the scans since then have been good news. The radiologist said: "We don't believe in miracles, but this sure looks like one."

Wim Koosterboer, survivor of hepatitis B and associated
liver cancer with lung metastasis



Robert Gorter, MD, PhD

Dr. Gorter trained in Amsterdam and for ten years served as physician, researcher, and then medical director of the Department of AIDS Epidemiology and Biostatistics, University of California, San Francisco Medical School, a department that provided world leadership in defining and treating AIDS. He has spent the past 25 years applying lessons learned from the AIDS epidemic and the emerging field of immunotherapy in the treatment of cancer. Dr. Gorter holds a medical degree in conventional Western medicine from the University of Amsterdam Medical School with postdoctoral work in the US, a PhD from the

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Nontoxic Cancer Therapy Utilizing Dendritic Cells

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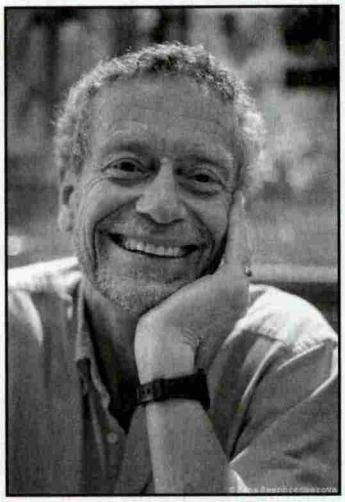
University of Witten/Herdecke in Germany, and specialty training in anthroposophical medicine in Switzerland with an emphasis on oncology. For more information on the Medical Center Cologne and for video interviews of patients in long-term remission, see www.medical-center-cologne.com.



Erik Peper, PhD

An internationally known expert on holistic health, stress management, and biofeedback, Erik Peper received his BA from Harvard University in 1968 and his PhD in psychology from the Union Graduate Institute in 1975. Since 1976 he has taught at San Francisco State University (SFSU), where he has been instrumental in establishing the Institute for Holistic Health Studies, the first program in holistic health at a public university in the U.S. President of the Biofeedback Federation of Europe and former president of the Biofeedback Society of America, he has written more than 200 journal articles and nine books, including *Make Health Happen*, and *Biofeedback Mastery*. In addition to teaching, research, consulting, and travel, he maintains a biofeedback practice in Berkeley, California. For additional information, see www.biofeedbackhealth.org and his blog site, www.peperperspective.com.

Resource: *Fighting Cancer: A Nontoxic Approach to Treatment*

This article is an excerpt from *Fighting Cancer: A Nontoxic Approach to Treatment* by Robert Gorter, MD, PhD, and Erik Peper, PhD, published by North Atlantic Books, *Fighting Cancer* presents the Gorter Model, a comprehensive treatment protocol that focuses on the body's intrinsic capacity for healing. This therapy was developed by Robert Gorter, MD, PhD, who in 1976 recovered from stage IV testicular cancer using these techniques rather than chemotherapy or radiation. Based on extensive research and decades of clinical practice, the treatment mobilizes the immune system with hyperthermia, injections of antigen presenting dendritic cells, the botanical mistletoe, nutrients and nutrient infusions, and lifestyle changes.

Nancy Faass, MSW, MPH

A writer and editor in San Francisco, Ms. Faass has worked on the development, writing, and editing of more than 45 books for publishers that include Elsevier, Harper, McGraw-Hill, North Atlantic Books, and others. Director of the Health Writers' Group, she also works collaboratively on articles, white papers, and writing for the Web and can be reached at info@HealthWritersGroup.com.

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The Integrative Cancer Toolbox

by Mary Budinger

Members of the International Organization of Integrative Cancer Physicians (IOICP) often see patients who have either been through the rigors of conventional treatment, or chosen not to go through surgery/chemotherapy/radiation because they have been told that they cannot tolerate it or because they have seen the damage done to others.

Often these patients come with depleted resources – physical, emotional, psychological, and financial. "We need to support these patients and rebuild them for the future while we treat the cancer today," said Annie Brandt, executive director of Best Answer for Cancer Foundation (IOICP is the physician arm of the foundation). "Each patient is individual, so some things work for one person but not for another. It is a very fine balancing act."

Integrative oncologists need a comprehensive toolbox to walk that tightrope. Some of those tools were on display at the foundation's 13th annual conference earlier this year in Reno, Nevada.

Systemic Enzymes

Enzymes and digestion go together like a horse and saddle, right? Yet perhaps just 1% of the enzymes in our body are used for digestion. The other 99% are the worker bees that put vitamins and minerals to work to speed up chemical reactions. These are the systemic enzymes; they circulate throughout the body.

"Enzymes are simple, powerful, yet often forgotten," said Donese Worden, NMD, of Arizona. "Sometimes we are so busy looking at the glitzy new therapies, we overlook the basics and enzymes are very efficient tools for cancer. For starters, using enzymes mean we help the patient to make more energy (ATP) with less effort."

In cancer, the powerhouse systemic enzymes are proteolytic (protein eating). The body manufactures trypsin and chymotrypsin. Other proteolytic enzymes such as papain, bromelain, serratiopeptidase, and nattokinase come from food or other outside sources. They can be formulated into supplements for healing purposes.

Proteolytic enzymes break down excess fibrin that has been linked to chronic systemic inflammation which feeds chronic diseases, including cancer. Enzymes are measured in units of fibrolytic activity, which means how much fibrin they break down in a set amount of time.

One school of thought has said that supplemental systemic enzymes contain molecules too large to cross the intestinal barrier. Yet studies showed that nattokinase can be measured in the blood after oral ingestion of a single capsule and that most proteolytic enzymes are absorbed.[1,2]

Studies have also shown useful modes of action. In colorectal cancer, systemic enzymes were found to prolong survival time and increase quality of life "by reducing both the signs and symptoms of the disease and the adverse reactions associated with adjuvant antineoplastic therapies."[3] In yet another study, the use of systemic enzymes "stimulated the production of tumor necrosis factor-α in human peripheral-blood mononuclear cell cultures in a time-dependent manner."[4]

Research is showing that serratiopeptidase, for example, can interfere with adhesion and invasion of eukaryotic cells and biofilm formation in staph bacteria.[5]

Enzymes also help with a most important issue for cancer patients – quality of life. Clinical studies reported in 2008 demonstrated that "systemic enzyme therapy significantly decreased tumor-induced and therapy-induced side effects and complaints such as nausea, gastrointestinal complaints, fatigue, weight loss, and restlessness and obviously stabilized the quality of life."[6]

Cancer creates its own ecological system and biofilms are one of its survival tools. "These biofilms surround tumors like a cloak and can prevent the immune system from recognizing and penetrating them," Worden said. "When we use proteolytic enzymes to break down the biofilm, many therapies appear to become more effective. Systemic enzymes carry very little risk and are easy for patients to take."

Silver

Many people with cancer have coinfections, especially viral and fungal. Silver is a time-honored tool for combating infections. It is a nontoxic, broad-spectrum antimicrobial therapy with no known toxicity and no known mechanism for acquired resistance.

The medicinal uses of silver have been documented since 1000 BC. More recently, silver is increasingly used as a disinfectant, impregnated into a variety of medical devices to prevent infections and their spread.

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The major mechanism by which silver nanoparticles have antimicrobial effects is by interacting with biochemical mechanisms in the bacteria and their cells walls.

A bioactive silver hydrosol can be used orally (under the tongue for 2–3 minutes), intravenously, in a nebulizer, as part of a rectal enema, instilled in the bladder by a Foley catheter, used intravaginally, in the eyes, and topically. Silver which has a positive charge is bound up by negatively charged chloride, and is processed through the liver's phase II detoxification pathway and excreted within 24 to 48 hours.

"In solid tumors with an active blood supply, bioactive silver hydrosol can work as an antiangiogenic agent by blocking new blood vessel formation," said Dr. Sean Devlin of Colorado, medical director of the Best Answer for Cancer Foundation.

But not all silver products are equal. Particle size and particle dispersion are key. Colloidal silvers and mixed salt forms can cause toxicity, including argyria, a benign cosmetic condition characterized by bluish or grayish discoloration of the skin. When silver particles cluster together, the body tries to eliminate them by excreting them through the skin and that leads to cosmetic discoloration. In products contaminated with salts, proteins, stabilizers, and oxidation, the silver particles tend to cluster rather than disperse evenly. These types of silver have little if any therapeutic effect.

"Buyer beware," cautioned Devlin. "You want a nano- and picoscalar pure silver suspension, meaning the silver is so small it hovers between matter and energy, proven through transmission electron microscopy (TEM). The particles are minute and uniformly dispersed for bioavailability and nontoxicity. In my protocols, I use Argentyn 23 hydrosol silver. It is one of the best antiseptics and has great tissue regenerative properties when used under the direction of a trained clinician. It is a staple in my toolbox."

PolyMVA

In the 1990s, Dr. Merrill Garnett discovered how to bind alpha-lipoic acid and thiamine (vitamin B1) to the trace mineral palladium by way of an electrical charge. That led to the development of the unique dietary supplement Poly-MVA, which has become a popular cancer tool with IOICP physicians because of its positive effect on mitochondria and proper cell division.

A human being is basically a bag of perhaps 80 trillion cells that make up our organs and tissues. Inside each of those cells are hundreds, even thousands of mitochondria. Think of them as tiny power plants where ultimately food is turned into energy (glucose) for everything that we do – high energy for the body to do the jobs we don't give a second thought to, such as kidneys filtering the blood, to the more obvious jobs like pressing our foot on the gas pedal or running. Binding thiamine and alpha-lipoic acid together guarantees they will arrive together at the start of the cellular electron transport chain where they are supremely qualified to enhance and protect the process of making energy (ATP) properly in the mitochondria.

"Simply put, when a cell starts to divide, the energy-making process alters and slows down, DNA unwinds, and the cell splits into two," explained Al Sanchez Jr., president of AMARC Enterprises Inc., which distributes Poly-MVA. "Then the mitochondria of the two new cells need to come back on line, start making energy properly, and get on with their jobs."

But it doesn't always work out that way. The body makes millions of "bad copies" or errant cells every day. Normally, cells try to repair themselves by engaging the p53 gene, messenger RNA, and other signaling molecules to trigger a cascade of events that starts the process of apoptosis (cell death), and the immune system is notified to dispose of them.

Cancer cells are abnormal cells that, for some reason, did not turn off or get killed. These cells still look to the body and the immune system like a healthy cell because they carry the same signature as the normal cell from which they were born, or perhaps they have managed to cloak themselves in biofilm. They hide from the immune system.

"Without the proper amount of energy, a cell cannot be repaired or thrive," Sanchez said. "Sometimes they morph, initiate, and stay stuck in a lifestyle that doesn't require normal cellular energy. It is as if they say, 'I'm just going to burn some sugar and not worry about producing energy like normal cells do. I don't need all that energy anyway because I don't have to do all the jobs that normal cells do. I am just going to stay in this lower energy (hypoxic) state to live and reproduce." A major difference with cancer cells is that they make and use smaller quantities of energy, with little need of oxygen, and simply keep fermenting sugars and producing lactic acid. They don't utilize the Krebs cycle to make high-energy ATP. By binding thiamine and alpha lipoic acid together, Poly-MVA is available at the start of the normal energy making process to create an energy/oxygen-rich cellular environment. This creates less opportunity for cell division to go awry, leading in some instances to dysfunctional/cancer cells."

When cells are energized, mitochondria and DNA are better supported and protected.

Oxygenated Therapies

Hydrogen peroxide (H2O2) and ozone therapies (O3) are an integrative tool which uses the same free radical killing mechanism that the immune system uses to eradicate foreign invaders. Cells make hydrogen peroxide to generate free radicals to kill errant cells, viruses, and bacteria.

"Hydrogen peroxide is cheaper for the patient, easier for the staff, and more user friendly in that a smaller needle can be used," said James Forsythe, MD, HMD, of Nevada. "I don't think oral peroxide has any value; it can be delivered intravenously. I am also impressed with some of the results of ozone. It can eliminate acute and chronic infections which often are part of the cancer picture."

"Oxygen, oxygen, oxygen is the key to healing because injured cells are starved for oxygen," said Robert Rowen, MD, of California. "Ozone, after it enters the body, breaks down into harmless water (H2O) and carbon dioxide (CO2)."

Rowen recently taught medical teams in Sierra Leone, West Africa, how to use ozone therapy to treat people infected with one of the most virulent pathogens, the Ebola virus. "Ozone is one of the best ways to inactivate viruses," he said. "Viruses have lipids and proteins in their structure that are highly vulnerable to damage by ozone. There is nothing else out there that will kill bacteria and viruses in seconds. It blows a hole in the cell membrane and the cell dies before it can repair itself. I really didn't expect in two short days that ozone would kill the most lethal virus in the world, but it did. I think hydrogen peroxide would have worked also."

One downside of IV ozone therapy is that it tends to irritate the lining of blood vessels, which is an issue for anyone with vein issues.

Oxidative therapy is an inexpensive tool that offers a broad spectrum approach to a wide variety of chronic infections and cancer, and one that is easily utilized by an integrative physician.

Non-Chemo-Based IPT

Most IOICP physicians use the hormone insulin to lower a patient's blood sugar prior to administering chemotherapy. As the blood sugar drops, the cancer cells become starved for sugar and open wide all their receptors (doorways to the inside of the cell). When the chemo arrives, followed closely by glucose, the cancer cells are hungry. They drink in the chemo in the effort to get at the accompanying sugar. It's like a Trojan horse effect. The insulin shuttles the drugs primarily to the cancer cells, largely bypassing healthy cells. That targeting, that use of insulin as a biological response modifier, is called insulin potentiation therapy (IPT). It gets the job done with perhaps 1/10 the dose of chemo used in conventional oncology.

Insulin also can be used as a biological response modifier to target the delivery of natural biological agents. A partial list includes curcumin, artemisinin, silymarin, resveratrol, oxidative therapies, oxaloacetate, methylglyoxal, methylene blue, Poly-MVA, and Argentyn silver. Each has a different mode of action, but they all make life inhospitable to cancer cells.

"No one will ever make the claim that these are as effective as chemo, because we don't use them alone and no has ever studied the synergies," said Juergen Winkler, MD, of California. "However, we know chemo drugs have resistance problems. Cancer can easily handle one attack – that is why eventually cancer cells become resistant to one drug. But if you approach it as an octopus and attack cancer multiple ways with multiple substances, it is easier to defeat, in my experience. I customize each treatment for the patient based on sensitivity tests from RCGG labs or Voll (electroacupuncture) devices."

Just as IPT's use of insulin targets chemotherapy directly to cancer cells, insulin also targets biological agents so they have a better opportunity of actually getting inside the cell to do their job.

"Most people who choose a non-chemo-based course of treatment with use of insulin as a biological response modifier are trying to find a less toxic way of treatment," Winkler said. "They have seen what chemotherapy's toxicity has done to family or friends. They don't get a lot of hope with conventional treatments, especially with advanced diseases. They realize that their quality of life is the important thing."

Hormones

Broda O. Barnes, MD, PhD, one of the world's foremost authorities on the thyroid gland, famously said, "Health begins and ends with the proper balance of the endocrine system." Barnes estimated that hypothyroidism affected as many as 40% of Americans in 1976. Since then, a national study showed that iodine levels in Americans have decreased 50% in the last 30 years. The body needs iodine to make thyroid hormones.

A 1977 study of 74 hypothyroid patients strongly suggested that thyroid hormone has a protective role in the prevention of cancer. Half the test subjects were treated with 2 or more grains of natural desiccated thyroid hormone; the other half got less than 1 grain or none at all.[7] In the treated group of 31 patients, there was only one case of cancer. In the untreated group of 43 patients, there were 32 cases of cancer.

"Most people with hypothyroidism do not get properly diagnosed because the standard lab test merely measures the amounts of TSH, T3, and T4 circulating in the blood," said Richard Pooley, MD, of Connecticut. Thyroid hormone exerts its effect inside the cells, not in the bloodstream. The blood levels of these hormones correlate very poorly with the actual thyroid activity in the patient.

"I work with the Broda O. Barnes Foundation where we send 24-hour urine specimens to Belgium to measure the levels of thyroid hormones (T3 and T4) along with cortisol and cortisol metabolites. This is arguably the best way of determining significant thyroid and cortisol deficiency. In the foundation's experience – which includes thousands of specimens and spans 3

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decades – every patient with cancer is both thyroid and cortisol deficient. The foundation has also had several patients with end-stage metastatic cancer who have been cured after supplementing with natural thyroid hormone and physiological doses of hydrocortisone."

After puberty, people typically experience fluctuations in their hormone levels. By age 35, levels tend to plateau and then decline. This is an invitation to cancer and other chronic health problems. When dealing with cancer, your adrenal glands also get depleted quickly and they don't have the robustness needed to deal with the illness.

"Hormones are more important than vitamins," said Pooley. "Although vitamins and other nutrients play an important role in the function of the immune system, balance of the endocrine system is usually the deciding factor influencing immune function. Thyroid hormone, and even cortisol (contrary to conventional wisdom), are the most important hormones for optimizing immune function, and immune function is the key element in the cure of cancer. The immune system, when properly optimized, destroys only the cancer cells without any collateral damage to normal cells."

Cancer Vaccine

There is much agreement in the medical community that cancer often involves a failure of the immune system to recognize and kill off errant cells. The immune system is our first and best defense against cancer, and many other chronic diseases. Can we unlock the power of the immune system to treat cancer by way of a vaccine made from stemlike cells of the immune system?

William Decker, PhD, Baylor College of Medicine, is on the leading edge of developing such a vaccine. The stemlike cells he works with are called dendritic cells and they are the generals of the immune system. They make all the decisions and send orders down the line. One of the platoons of soldiers down the line are the Th1 cells, part of the acquired immune system that goes after intracellular viral and bacterial infections.

"The Th1 cells are generally not very active in people with cancer and yet Th1 immunity is most important in cancer," said Decker. "We can help the body prime a more robust Th1 response by helping it recognize patterns important to the functioning of a virus or intracellular bacterium."

Decades ago, it was noticed that spontaneous tumor regression has followed many different types of infections. It is thought that these infections "wake up" the immune system by sending appropriate signals for a Th1 immune response to kick in. Cancer antigens may come along for the ride during such infections and result in spontaneous remissions.

"One of the proteins in dendritic cells is CTLA-4 (cytotoxic T-lymphocyte associated protein 4), the most famous immune regulatory molecule in the universe," said Decker. "Only very recently discovered to be expressed by dendritic cells, we now know dendritic cell CTLA-4 controls whether lymphocytes (a type of white blood cell) are turned off or on during the initiation of an immune response. Normally, CTLA-4 signaling regulates the immune system by turning off lymphocytes so you don't get an inappropriate immune response. With cancer, if you block the activity of CTLA-4, you can turn on important downstream effects in generating CD8 T-cells which can kill cancer cells. CD8 T-cells are more functional when we get CTLA-4 out of the equation."

Decker and his team at Baylor are in development with a vaccine to downmodulate CTLA-4 expression. "CTLA-4 exists in dendritic cells; it is real, we have documented it. Other vaccines, targeting other modes of action, have possibly not performed well because even though they make an immune response against a specific protein, they don't address dendritic cell CTLA-4. What we are developing is a way to make the dendritic cells mimic something you typically only get with a real viral infection."

Conclusion

Thomas P. Hsia, MD, of California, is board certified in gastroenterology. He came to the conference thinking he would attend just the ozone seminar but decided to stay and check out the presentations. He was blown away.

"It opened my eyes to a lot of options out there," Hsia said. "As a mainstream professional, I was interested to see the validity and justification of my belief system that all disease – be it autoimmune, heart, diabetes, or cancer – is all part of the spectrum of too much toxicity (heavy metals, pesticides, toxic emotions) and too many nutritional deficits. Often in my world, the kind of information presented at this conference is considered interesting but something to ignore because there are so many points of departure from the conventional model in which we are trained. I am fascinated with all this information and the research behind it all."

Mary Budinger, NTC, is a certified nutritional therapist and an Emmy-award winning journalist. She teaches about nutrition and integrative medicine in Phoenix, Arizona; 602-494-1999.

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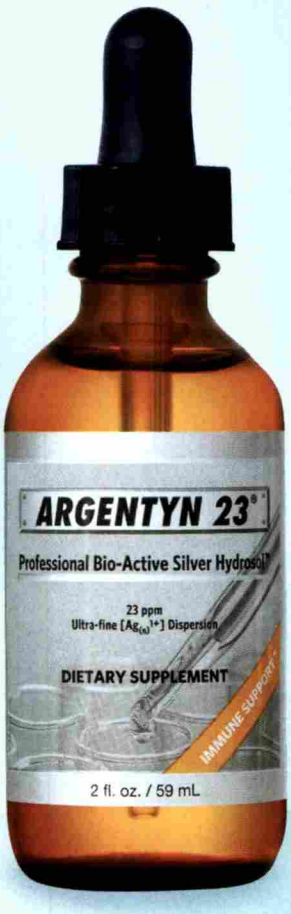

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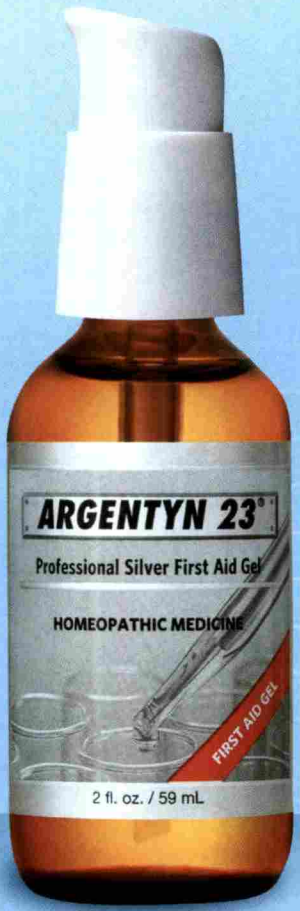

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Cancer and Lyme Disease: Is there a Connection?

by Nooshin K. Darvish, ND, FICT

> There is a sign (from God) in every phenomenon: The sign of the intellect is contemplation and the sign of contemplation is silence, because it is impossible for a man to do two things at one time – he cannot both speak and meditate.
>
> ʿAbdu'l-Bahá. *Paris Talks*, 1844–1921

Introduction

In 1911, Peyton Rouse discovered a viral etiology for cancer and won a Nobel Prize for his work 50 years later. Despite this discovery, cancer therapy continues to be based on the perception of cancer as the "phenomenon." As such, the majority of current conventional and alternative oncological treatments often neglect possible causative agents, including viruses, spirochete and other bacteria, molds, and other parasites. Since 1975, conventional radiation and chemotherapy, along with efforts and funds placed into cancer research, have not significantly decreased incidence rates, or mortality from cancer, especially in women.[1,2] Decades of emphasizing the eradication of tumors as the treatment goal has evidently not provided significant benefit to the obliteration of cancer in general.

We must instead look at cancer from a different perspective in order to obtain more successful results. By addressing cancer as a sign, which signals underlying phenomena and thus continuing on the path that Rouse began in 1911, we will achieve the results that we have been seeking for decades. A natural progression of Rouse's work is to understand the unhealthy milieu within the tissues, which creates an environment appropriate for the invasion of viruses, parasites, and other infections, which in turn lead to cancer growth. I propose that a diseased milieu is the union of contributing factors, specifically psychoemotional trauma, toxicities, and intracellular spirochetes and their coinfections. Together these contribute to a weakened immune system, which no longer combats cancerous cells and therefore leads to tumor growth. This article will focus on spirochetes and their coinfections and their link to cancer growth and metastasis.

Multiple Systemic Chronic Infection Syndrome (MSCIS)

As multiple systemic chronic infection syndrome (MSCIS), also known as chronic Lyme disease, progresses into late-stage disease, various systems and infections become involved. Because of its nature as an intracellular spirochete, similar to HIV as an intracellular virus, the *Borrelia* species and its family

of coinfections reduce the function and number of T cells, mainly natural killer cells in many patients. This is often seen as reduced CD8-57 on laboratory testing. These patients often exhibit other signs and abnormal laboratory test results as seen in Table 1. Hormonal imbalances and stage 2 or greater adrenal fatigue syndrome commonly contribute to chronic fatigue in these patients.

Beyond the immunological, metabolic, and hormonal disturbances caused by MSCIS, mitochondrial and autonomic nervous system dysfunctions are common and lead to chronic fatigue, cardiac disorders, and neuropathy. Enzymatic and detoxification abnormalities and nutritional deficiencies often complicate healing and lead to further pathological conditions in MSCIS. The presence of toxicities, including chemical, metals (for example: mercury, aluminum, lead, cadmium and arsenic), mycotoxins, neurotoxins, biotoxins, and biofilm result in significant neurological, musculoskeletal and digestive symptoms and pain. Allergies and severe hypersensitivity reactions to food, environmental agents, electromagnetic fields, light, and sound plague many of these patients, as do digestive disorders such as small intestinal bacterial overgrowth, leaky gut syndrome, candidiasis, and parasitic infections. Furthermore, as the disease progresses, there is a worsening of sleep disorders, psychoemotional issues, chronic pain, and cachexia.

The signs and symptoms of late-stage MSCIS, as described above, mimic the signs and symptoms of late-stage cancer patients. Because these signs and symptoms of MSCIS are identical to those of late-stage cancer, the possibility then exists that MSCIS plays a pivotal role in the etiology of cancer. My clinical experience verifies that those cancer survivors whose lifespans were considerably prolonged and whose quality of life improved significantly, as compared with their respective counterparts treated by conventional methods alone, were diagnosed and treated for MSCIS. Examples of patients with aggressive cancers, such as pancreatic cancer, grade IV glioblastoma, stage 3 serous carcinoma of the uterus, stage 4 myxofibrosarcoma, stage 4 invasive ductal carcinoma, chronic myelogenous leukemia, stage 4 colon cancer, and many others once diagnosed and treated for MSCIS, have resolution or stabilization of their cancers as evidenced at my clinic.

Chemotherapy as Antimicrobial Therapy

The fact that patients with successful conventional treatments of their cancers do exist points to the concept that several of the chemotherapeutic agents also act as antimicrobial agents. Oncologists may not be aware that some chemotherapy agents act as strong antimicrobial agents; cisplatin and adriamycin, for example, reduce not only the cancerous load but also the infectious load of MSCIS. Cisplatin has antimicrobial activity against gram-negative and gram-positive bacteria, as well as against yeast and mold (see Table 2). Twenty-one chemotherapeutic agents with antimicrobial activity against four different microbes are listed in Table 3 (p. 54). Further evaluation of chemotherapeutic agents and their antispirochete activity is needed to understand their efficacy in cancer patients with MSCIS. These antineoplastic agents appear to decrease the infectious load in cancer patients and MSCIS patients. Thus, the fact that some patients do have success with conventional cancer treatments may be attributed to the antimicrobial rather than the antineoplastic properties of utilized chemotherapeutic agents.

Antimicrobial Therapy with Antineoplastic Benefits

The use of antibiotics appears to increase the risk of breast cancer.[5] Velicer et al. outline the use of antibiotics associated with an increase risk of breast cancer due to the fact that antibiotics cause disturbances in immune function, inflammation, and estrogen metabolism.[4] The study does not discuss causal effects of antibiotics and cancer, nor does it discuss particular antibiotics. Certain antibiotics and antimicrobial medications have been shown to induce apoptosis to individual cancer cells lines.[6,7,9,11] Therefore, one would infer that these particular antimicrobials decrease cancer risk, though this needs further investigation. The possibility then exists that effective antibiotics specifically against borreliosis and its coinfections may reduce cancer risk, which also requires further investigation.

Interestingly, fluoroquinolones exhibit antineoplastic behavior through inhibiting DNA replication, causing mitochondrial damage and inhibiting topoisomerase activity. Ciprofloxacin is not only effective against borreliosis but has shown to cause apoptosis to colorectal cancer cell lines.[6] Potential exists for quinolones to be used as effective antineoplastic agents in cancers including bladder cancer.[7,8]

Fungal infections and mold toxicities play an important role in the symptomatology and possible disease progression of MSCIS as well as cancer. Ketoconazole is a potent antifungal and exhibits effective chemotherapeutic activity in metastatic prostate cancer.[9,10] *Mycoplasma* is a coinfection of borreliosis and plays a significant role in lung cancer.[12] Antifungal medications, therefore, may prove to be an effective treatment for lung cancer.

Parasitic infections often are found in patients with cancer as well as those fighting MSCIS. Antiparasitic drugs including mebendazole and all "-azoles" appear to elicit strong antitumor

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Table 1: Abnormal Laboratory Results in MSCIS

↑	Inflammatory markers (IL-1, IL-6, CRP, Ferritin, TNF-α
↓	Platelets
↑	Liver Function Tests
↑	Coagulability
	Insulin Resistance
	Abnormal Lipid Panel
	Abnormal Alkaline Phosphatase
	Normal/Abnormal Thyroid function
↓	Salivary DHEA
↓↑	Salivary Cortisol
↓	Salivary Progesterone
↓	Testosterone

Table 2: Antimicrobial Effects of Cistplatin

Gram positive: *E. coli, Klebsiella p., Pseudomonas a., Proteus m., Serratia m.*

Gram positive bacteria: *Streptococcus, Staph aureus, Neisseria catarrhalis*

Yeast and mold: *Saccharomyces c., Schizosaccharomyces, Candida albicans,* and *Dictyostelium d.*[3]

Table 3: Activity of 21 antineoplastic agents against 4 groups of pathogenic microorganisms, expressed in semiquantitative terms

Antineoplastic Agent	Activity against indicated type of organism: Gram-positive bacteria	Gram-negative bacteria	Anaerobic bacteria	Yeasts
Alkylating agents				
Carmustine	0	0	0	±
Chlorambecil	0	0	±	±
Neoplatin	0	+	ND	0
No activity shown by busulphan, cyclophosphamide, dibromomannitol, and melphalan.				
Antimetabolites				
Aminopterin*	+ + / ±	±	+ +	±
Azathioprine	0	0	+	0
5-fluorouracil*	+ + + / + +	±	+	+
Methotrexate*	+ + / ±	0	0	±
Thioguanine	±	±	±	0
No activity shown by cytarabine, mercaptopurine.				
Inhibitors of cell division				
Etoposide	+	0	+	0
Vinblastine	±	0	ND	±
No activity shown by vincristine.				
Antibiotics				
Doxyrubicin	0	0	+	0
Mitomycin C	+ + + +	+ +	+ + + +	0
Miscellaneous				
Dacarbazine	±	±	+	0
Hydroxyurea	0	±	0	0
Procarbazine	±	0	0	0

Key: + + + + represents MIC in the range 0.01 – 0.1 mg/ml
+ + + 0.1 – 1
+ + 1 – 10
+ 10 – 100
± 100 – 1000
0 >1000
ND not determined

*Aminopterin, methotrexate and 5-fluorouracil showed significantly higher activity against *Strep faecalis* than against staphylococci, hence two scores in "Gram-positive" category.

Minimum inhibitory concentrations (MIC) of four antineoplastic compounds against different groups of bacteria

Compound	MIC against bacteria (ug ml) Range of values observed: *Gram-positive* *Staphylococci*	*Streptococcus faecalis*	*Gram-negative*	*Anaerobes*
Mitomycin C	0.06 – 0.25	0.06	0.5 – 8	0.05 – 0.5
5-fluorouracil	0.5 – 8	0.13 – 0.25	≥256	10 – 100
Aminopterin	256 – 1024	8	256 – 512	1 – 10
Methotrexate	64 – 1024	8 – 16	>1024	>100

Source: J.M.T. Hamilton-Miller. Antimicrobial Activity of 21 Anti-neoplastic Agents, *Br. J. Cancer* 1984;49:367–369.

Table 4: Examples of Herbal Extracts with Antimicrobial and Antitumor Effects

Andrographolides (*Andrographis paniculata*)
Oleuropein, hydroxytyrosol (Olive Leaf Extract and oil)
Berberine alkaloids (*Hydrastis canadensis, Berberis aquifolium, Coptis chinensis, Berberis vulgaris, Berberis aristata)*
Artesunate (artemisinin)
Uncaria tomentosa extract

activity both in vivo and in vitro, making them effective agents in cancer patients with MSCIS. The "-azoles" appear to inhibit cystoplastic microtubule formation and replication leading to apoptosis, deter glucose uptake by cells without affecting serum glucose levels, target cancer cells and helminthes, and impede neovascularization in vitro and in vivo.[11]

Natural Antimicrobials with Antitumor Activity

Multiple herbal antimicrobials addressing bacteria, fungi, viruses, and spirochetes also exhibit antitumor activity, making them effective in the treatment of cancer and MSCIS. Examples of such herbs are found in Table 4. Many of these herbs show efficacy in the treatment of Lyme disease and potentiate adjunctive cancer protocols, often acting as antiangiogenesis modulators, inhibiting tumor replication, causing cancer cell arrest and apoptosis, downregulating inflammation and VEGF (vascular endothelial growth factor), and reducing platelet aggregation. Herbal extracts, such as andrographolides from *Andrographis p.*, and oleuropein and hydroxytyrosol from olive-leaf extract and its oil, as well as berberine alkaloids, have greater benefits beyond their antimicrobial, cytotoxic, antineovascularization, immune-modulating, and anti-inflammatory effects in cancer and MSCIS. These extracts exhibit powerful protection of the liver and kidneys from chemotoxicity, thus making them important adjunctive therapies in cancer.

Clinical Cases

The following clinical cases, from personal experience, exemplify the benefits of evaluation and treatment of MSCIS in cancer patients.

A 57-year-old male with grade IV glioblastoma, the most aggressive form of brain tumor, was given a 6-month prognosis. However, he survived over 7 years once he was diagnosed with neuroborreliosis and treated for Lyme disease and MSCIS using naturopathic and integrative medicine with a non-antibiotic-based protocol.

A 46-year-old female with stage 4 myxofibrosarcoma involving bone metastasis was told that she needed amputation of her thigh in order to survive. Once she was diagnosed with MSCIS and treated accordingly using herbal and natural therapies, her tumor significantly regressed after 3 months of treatment. Because she no longer had bone metastasis, leg amputation was no longer indicated and was not performed. Today, she walks normally and is in remission.

A 58-year-old female with chronic myelogenous leukemia of 10 years and recent diagnosis of invasive ductal carcinoma of the breast had complete regression of both of her cancers after she was diagnosed and treated for MSCIS using an integrative non-pharmaceutical-based protocol.

Conclusion

Oncological patients should be evaluated and treated for multiple systemic chronic infectious syndrome. The immunodeficiency that occurs in MSCIS increases the risk of cancers. To have effective treatments for cancer, conventional therapies involving chemotherapy and radiation are not sufficient. Multiple infections involving spirochetes, bacteria, viruses, parasites, and fungi, found in cancer patients necessitate the use of herbal and pharmaceutical antimicrobial

agents. The complexity of oncological patients demands further research to investigate the presence of hidden MSCIS in every cancer patient if we are to make advancements in cancer mortality and incidence, and to improve quality of life. Cancer is not a phenomenon but a sign signaling a diseased milieu, directing us to evaluate the underlying disease progression through a more thorough evaluation and treatment of MSCIS.

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Targeting the IGF-1 Pathways

by Jacob Schor, ND, FABNO

Introduction

Insulin-like growth factors (IGFs), especially IGF-1, are of interest because they may explain why many of the therapies that naturopathic doctors have traditionally relied upon with cancer patients may actually work. Understanding IGF function may allow us to optimize current dietary and lifestyle strategies in treating cancer as well as inform dietary recommendations for treating other conditions.

Background

Insulin-like growth factors 1 and 2 are proteins produced by the liver in response to growth hormone produced by the pituitary gland in the brain. These growth factors stimulate development of somatic tissues, in particular skeletal, muscle and bone. In the last 25 years, extensive research has focused on the role IGFs play in cancer and longevity.[1]

Salmon and Daughaday first hypothesized the existence of the IGFs back in 1957 as they searched for growth hormone (GH) mediators, initially naming the two IGFs "somatomedins A and C."[2,3]

Significant amounts of IGF are present in the blood, up to 1 mcg/ml, higher concentrations than other hormones. Most IGF is bound to one of six different IGF binding proteins (IGFBPs). These binding proteins regulate the amount of free IGF available to bind to IGF-receptors (IGFRs) on cells. This process is complicated; these binding proteins may lower free IGF serum levels but some also compete for IGF receptor sites and some amplify IGF function.

Both IGF-1 and IGF-2 bind to the IGF-1-receptors, while only IGF-2 binds to the IGF-2-receptor. This second receptor does not appear to do much so is generally ignored (and this may be a mistake).

IGFs mimic insulin in many ways; they increase glucose metabolism, increase glucose transport, inhibit fat breakdown, and increase lipid synthesis, all actions that are "like insulin" but always to a weaker degree than insulin.

IGF-1 plays a central role in cellular growth, differentiation, survival, and cell cycle progression. It is expressed early in life; it's why babies grow bigger.[4]

IGFs are curiously not essential for survival. Mice bred without IGF survive but are about half the size of their siblings.[5] The drastic variation in size between dog breeds is because of IGF-1 polymorphisms.[6]

IGF-1 and Cancer Link

Two things pointed to a role of IGF-1 in cancer. People with a genetic disorder causing an IGF-1 deficiency have a very low risk of cancer. Second, epidemiologic data suggest that IGF-1 levels or IGF-1 binding protein levels may be predictive of cancer risk.

In 1966, Israeli endocrinologist Zvi Laron described a genetic condition, which has been since named after him, in which infants are born both deficient and resistant to IGF-1. These babies grow slowly and remain small; as in the IGF-1 deficient mice, about half the size of normal adults.[7,8] A cluster of these patients living in a single village in Ecuador was discovered in the 1970s.[9,10] Both the initial Israeli patient population that Laron first reported and these Ecuadorians are descendants of Spanish Jews driven out by the Inquisition. Researchers have now tracked the health of 100 of these Ecuadorian Laron syndrome patients for over 2 decades. These individuals do not get diabetes, and rarely if ever get cancer.[11] This observation led Harvard researchers to examine epidemiological data, asking whether IGF-1 was predictive of cancer occurrence and prognosis.

In 1998, Chan reported that plasma IGF-1 concentrations were positively associated with development of prostate cancer. Chan also reported that IGFBP-3 levels were inversely associated. The more of this binding protein, the less free IGF-1 would be available to bind to and activate the IGF-1-receptors. Further studies reported a similar reciprocal association between IGF-1 and IGFBP-3 in other cancers including breast, colorectal, and lung.[12] More studies quickly followed; high IGF-1 levels were associated with increased risk for most, if not all, cancers, including prostate, colorectal, multiple myeloma, breast, lung cancer, thyroid, bone, brain, and ovarian.[13–22] This IGF-1 link to cancer explained why tall children are at greater risk for all types of cancer later in life.[23,24] In people who have had cancer, low IGF-1 levels may predict longer survival.[25] All this was exciting: IGF-1 and its pathways offered a clear target for cancer prevention and treatment.

Waning Benefit

This initial surge of excitement over the IGF-1 waned a bit in the early 2000s; not all studies found IGF-1 to be as strongly correlated as the first evidence suggested. In fact, it seems that in recent years, the stimulatory effect of IGF-1 on cancer weakened. (This writer suspects this may in part be due to changing dietary habits, in particular increasing carbohydrate intake and resultant increasing prevalence of metabolic syndrome and hyperinsulinemia may account for this shift, but has yet to find published data to support this theory.)

A 2004 meta-analysis by Andrew Renehan, including 21 eligible studies and comparing 3609 cases against 7137 controls, reported that high IGF-1 levels were associated with only a modest increased risk for prostate cancer (odds ratio: 1.49) and for premenopausal breast cancer (OR: 1.65). IGFBP-3 levels were associated with increased risk of premenopausal breast cancer (OR: 1.51) but not postmenopausal.[26] In a second meta-analysis two years later, Renehan again only found modest associations, still finding IGF-1 and IGFBP-3 useful in predicting premenopausal but not postmenopausal breast cancer. In 2006 Rinaldi, using data from the EPIC cohort, reported no association in younger women but a positive association for both IGF-1 and IGFBP-3 in women older than 50 years. Eva Schernhammer, using data from the Nurses Health Study II, found no significant associations. In a 2006 commentary, Renehan pointed out that the association between IGF-1 and diagnosis of cancer appeared to be weakening with the passage of time. Still, even in their 2006 analysis, women with high IGF-1 had a 69% greater risk of being diagnosed with breast cancer.[27] Roddam, in a 2008 meta-analysis, reported that doubled circulating IGF-I levels, were associated with only a 35% increased risk for prostate cancer.[28]

Recent studies still do suggest benefits of low IGF-1 for cancer patients. Duggan et al. in 2013 reported that a high IGF-1/IGFBP-3 ratio in women with a history of breast cancer was associated with nearly triple the risk of dying from any cause.[29]

Unlike some other carcinogenic pathways (such as HER2), mutations of the IGF-1 receptor are not linked to particular cancers. IGF-1 is not oncogenic itself; rather, IGF1-receptor "... signaling appears to be necessary but not sufficient for cancer growth."[30] IGF1-receptor signaling appears more important in preclinical experiments, results of the "... human clinical trials have been less promising. Despite evidence of some activity in early phase trials, randomized phase III studies have thus far been unable to show a benefit of blocking IGF signaling in combination with conventional strategies. ... This inability to translate the preclinical findings into useful clinical strategies calls attention to the need for a deeper understanding of this complex pathway."[43]

Ways to Lower IGF-1

- Fasting
- Caloric restriction[80]
- Reduce animal protein
- Decrease milk and whey proteins[81]
- Mediterranean diet[82]
- Proton pump inhibitors[83]
- EGCG[84]
- Metformin[85]
- Curcumin[86]

Ways to Increase IGF-1

- Prunes[92]
- Deer antler[93]
- Meat
- Protein: any[94]
- Methionine[95]
- Milk and whey proteins[96]

IGF-1 Is Not All Bad

There are situations in which increasing IGF-1 is advantageous. As mentioned, using drugs to block IGF-1 activity leads to problems. That's because we need IGF-1 to maintain healthy vasculature, cognitive function, and bone strength.

We may want to increase IGF-1 to treat neurodegeneration, stroke, CVD, Alzheimer's disease, osteoporosis, and injury.[87–91]

in the growth of carcinomas than in adenomas, particularly in carcinomas that have become resistant to HER2 or EGFR inhibitors.[31,32] In speaking with patients I often employ an analogy and liken IGF-1 to Miracle-Gro Plant Food: "It makes what is already there grow faster."

Drugs

IGF-1 receptors became an obvious and exciting target cancer drug development.[33–35] Over two dozen monoclonal antibodies targeting IGF-1-receptors have been developed and researched against a range of cancers, including sarcoma prostate, thymus, colorectal, pancreatic, brain, lung, squamous cell, and breast.[36,37] Many of these have already reached human trial, including figitumumab, ganitumab, conatumumab, cixutumumab, and dalotuzumab.[38–42]

While the concept of attacking these IGF pathways looked so exciting

Researchers used the word *futile* in describing their attempt to improve outcome in a clinical trial of figitumumab in NSCLC patients when they announced they were discontinuing the trial last year.[44,45]

"The optimal strategy for targeting IGF signaling in patients with cancer is not clear. The modest benefits reported thus far underscore the need for a better understanding of IGF signaling, which would enable clinicians to identify the subset of patients with the greatest likelihood of attaining benefit from this targeted approach." [46]

While the IGF theory sounds great, the drugs have not delivered the expected or promised results.[47,48] This may be due to several reasons. First, the drugs may just work too well; IGF-1 plays an important role in preserving health and totally blocking its activity may backfire. Second, the

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IGF-1 Pathways

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IGF receptors are also sensitive to insulin; and unless insulin is lowered in tandem with IGF-1, something that the drug trials have not considered, we may not see benefit.

Diet needs to not only be considered when attempting to influence IGF-1's role in cancer, it may actually be the more effective way to address this pathway. We can use dietary interventions to lower IGF-1, and we should at the same time also use diet to lower insulin production.

Serum IGF-1 levels increase with animal protein consumption and decrease as consumption is lowered. Dairy protein appears to have the greatest impact. Moderate decreases in animal protein may have greater impact on IGF-1 levels than extreme decreases. Many patients appreciate the news that they need not become absolute vegans.

Two recent studies of particular interest related to IGF-1 are Levine's 2014 paper on animal protein consumption and longevity and Millman's on IGF-1 levels in old age.

Levine reported that high dietary protein intake during middle age increases morbidity and mortality; high-protein diets are associated with a 75% increase in overall mortality and a 4-fold increase in risk of cancer death. Low protein during middle age is associated with lower mortality. The authors attribute all these effects to dietary protein raising IGF-1.[49]

Milman found that low IGF-1 levels as useful in predicting longevity.[50] For women in their 90s, those with IGF-1 below the group's median lived longer than those with above average levels. In elderly men, in contrast to the women, low IGF-1 is associated with increased mortality. High circulating IGF-I bioactivity in old men is associated with extended survival because of reduced cardiovascular risk.[51]

A third paper has also been on my mind, particularly when speaking with breast cancer patients, since it was published in April 2014. This is Jennifer Emond's landmark paper on breast cancer, IGF-1-receptor status, and diet. Emond's team compared the effect of decreased carbohydrate consumption on breast cancer recurrence rates in women whose tumors were classified as either positive or negative for IGF-1-receptors (IGFR). Receptor status made a significant difference in their outcome.

Dietary carbohydrate intake had no significant effect on women whose tumor cells were IGF-1-receptor negative, but for women who were positive, it made a huge difference. Those women, who maintained the same level or increased their carbohydrate intake, had over a 5-fold increased risk of recurrence. For these IGF-1 receptor positive women, lowering carbohydrate intake was associated with an 80% decreased risk of recurrence. Emond considered a 10% reduction in calories from carbohydrates as "low carb."[52] Dietary interactions, particularly with carbohydrates, may be the missing piece of the IGF puzzle.

Few evaluations of the impact that IGF pathways have on cancer have included the effect of insulin. This perhaps, was a mistake. Insulin-like-growth factors not only look and act like insulin structurally but there is a great deal of what scientists call crosstalk between the receptors that these hormones bind to. Insulin and IGF-1 bind to each other's receptors. Insulin receptors (IR) are also overexpressed in cancers and they form hybrid receptors that are a cross between IGFR and IR so that both insulin and IGF-1 will activate them.[53] Insulin itself becomes a potent growth factor promoting cancer proliferation. High insulin levels also increase the bioactivity of IGF-1 by inhibiting IGF binding protein-1.[54]

This annoyingly complex group of interactions between the different forms of insulin, IGF and IR and IGF-receptors all act together influencing behavior of cancer cells, their growth rate, and their tendency toward apoptosis.[55]

This could explain the inconsistencies in data seeking direct correlation between any one of these hormones and cancer outcome and also the modest outcomes reported only using antibody drugs that target only IGF-receptors.[56]

As we often find in biology, few of the actors are all good or all bad. While stimulation of IGF-1-receptors may have an unwanted impact on cancer and longevity, IGFs still play an important role in keeping people alive. IGF-1 is important in maintaining healthy vasculature (particularly when vitamin D levels are low), cognitive function, and bone architecture.[57] Thus we may actually want to increase IGF-1 levels in particular situations. IGF-1 protects the brain from aging and neurodegeneration; reduces risk of stroke, dementia, and Alzheimer's disease; helps stroke patients recover faster; and prevents osteoporosis.[58–62]

There are clearly times when our goal should be to increase IGF levels and IGF-receptor activation. For preventing and slowing cancer growth though, our goal is clearly the opposite.

It should be mentioned somewhere that lowering IGF-1 through short-term fasting is a well-known way to reduce the side effects of chemotherapy.[63] Lowering IGF-1 during chemotherapy, and possibly radiation, may also enhance treatment effectiveness.[64]

At this point the best-documented way to lower IGF-1 is through caloric restriction.[65–67] Reducing animal protein consumption, as mentioned, also lowers IGF-1.[68] In humans, reducing protein consumption actually lowers IGF-1 more effectively than caloric restriction. Interestingly, moderate protein restriction appears more effective than severe restriction in reducing total and free IGF-1 levels. Reducing protein intake from an average of 1.67 to 0.95 g/kg/ body weight/day for 3 weeks reduced serum IGF-1 from 194 ng/mL to 152 ng/mL.[69]

High-protein diets will not increase IGF during total energy deficit.[70] That

is, any diet without adequate calories to maintain weight will not raise IGF-1. Following a Mediterranean-style diet, particularly one with less meat, also lowers IGF-1.[71]

Milk and whey protein consumption increases IGF-1 significantly.[72,73] This might explain milk's association with prostate cancer.

Metformin, the drug commonly used to treat type 2 diabetes, may be useful against cancer in part because it lowers IGF-1 through "the activation of the AMP-activated protein kinase (AMPK) ... leading to reduced circulating insulin levels and decreased insulin/IGF-1 receptor-mediated activation of the PI3K pathway." Metformin increases insulin sensitivity lowering insulin levels. Hyperinsulinemia, as mentioned, increases the bioactivity of IGF-1 by inhibiting IGF binding protein-1.[74]

IGF-1 maintains bone health and, not surprisingly, some of the factors used to increase bone density also increase IGF-1 levels.[75] Diets high in dried plums (i.e., prunes) increase bone density by increasing IGF-1.[76,77] Vitamin D increases IGF-1 levels in adults.[78] Curiously, proton pump inhibitors sharply lower IGF-1.[79] (These drugs increase bone fracture risk, and the past assumption was that they interfered with calcium absorption. Perhaps it is their effect on IGF-1 levels that weakens bone?)

At this point information on IGF pathways is less clear cut than we might wish, but for cancer patients our focus should clearly be on reducing IGF-1 bioactivity. Caloric restriction, intermittent fasting, animal protein reduction (particularly dairy protein), and making food choices modeled after a Mediterranean diet will help do this. Preventing hyperglycemia and hyperinsulinemia by reducing carbohydrates may also be key to seeing benefits; the less IGF-1 and the less insulin, the better.

IGF-1 chemistry and insulin cross-talk is cutting-edge biochemistry, but the bottom line remains close to what we naturopathic doctors have traditionally told our patients to do: cut down on animal protein, especially dairy; decrease sugar and simple carbohydrates; lose weight; exercise; and follow a Mediterranean-style diet.

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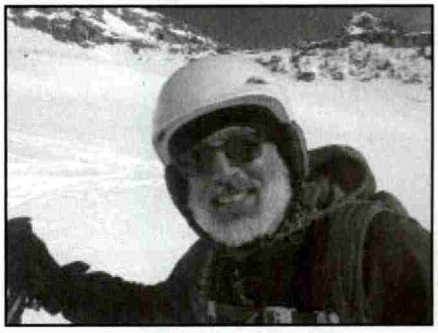

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The Almost Perfect Chemotherapy

by Reagan Houston, MS, PE

Chemotherapy is widely used but only moderately successful. We have spent billions of dollars, but improvements have been slight. Are we doing something wrong? What might the perfect chemotherapy be like? (Table 1)

Table 1: The Aim of Almost Perfect Chemotherapy

1. Control all cancers regardless of type or stage.
2. Strengthen normal cells without causing bad side effects.
3. Cause no pain.
4. Decrease the pain from active cancer.
5. Be clinically tested and safe.
6. Be available to patients now without government restrictions.
7. Strengthen the immune system to control other diseases.

The idea of the Almost Perfect Chemotherapy (APC) started with an article by L. Benade at the National Cancer Institute in 1969.[1] He reported that ascorbate (vitamin C) killed one type of cancer in vitro, and suggested that future studies of chemotherapy "rest on the use of ... host-nontoxic compounds that are lethal to cancer cells of which ascorbate ... represents an excellent prototype." The NCI neglected vitamin C as a therapy.

The APC grew with Drs. Ewan Cameron in Scotland and Linus Pauling in the US.[2] They treated hundreds of patients with many types of cancer at various stages with high doses of vitamin C. Their results were fairly good when Cameron gave bedridden cancer patients intravenous (IV) vitamin C for 2 weeks and then orally and continually. Creagan and then Moertel partly repeated Cameron's regimen without the IV vitamin C.[3,4] Their results did not show vitamin C as helpful, and this gave vitamin C a bad reputation.

The third step by Abram Hoffer, MD, PhD, and his multivitamin regimen for cancer was successful (Table 2).[5] To vitamin C, he added supplements that were either vitamins or vitaminlike compounds (made by the body). Hoffer knew that vitamins work better if used together. For example, vitamins C and E each kill cancer in vitro, but if used together they can be up to 50 times as effective as either alone.[5] The work of Drs. Ronald Hunninghake and Linus Pauling added other vitaminlikes.[6,7]

To strengthen itself, the body makes several therapeutic vitaminlikes. These include lipoic acid, coenzyme Q10 (CoQ10), L-carnitine, and lysine. Hoffer developed doses good for cancer therapy and those doses are often similar to therapy for other illnesses.

All of these supplements are available from health food stores. Hopefully the vitamins and other supplements selected are sufficient to control many diseases. None require a prescription. This article is not a complete or exclusive list of vitamins and vitaminlikes, as our immune system frequently provides several solutions to each illness.

Hoffer's Multivitamins

Vitamins, vitaminlikes, and essential minerals alone do not make an Almost Perfect Chemotherapy. A diet with too much sugar or processed carbohydrates that turn into sugar ➤

Table 2: The Almost Perfect Chemotherapy

	Daily pills
Abram Hoffer[5]	
Vitamin C	3000–12,000 mg
Vitamin E succinate natural	800 IU
Vitamin D3	5000 IU
CoQ10, ubiquinol*	200 IU
Ronald Hunninghake[6]	
Lipoic acid*	300–600 mg
Acetyl-L-carnitine*	2000–3000 mg
Linus Pauling[7]	
Lysine *	3000–6000 mg
Lesser Items[2,5]	
Multivitamin, (vitamin A selenium, zinc)	1 or 2
Vitamin B complex	B50
Fish oil pill	1000 mg

Diet[5]

More omega-3 fatty acid & water. Less processed carbohydrates, sugars. Less hydrogenated fats.

*vitaminlikes

➤

can put enough glucose into the blood to hinder vitamin C from entering cells.[2,8] The long-term use of hydrogenated fats can stiffen the semipermeable membranes around each cell in the body to limit the flow of food (glucose) into the cells.[8,9] This lack of food may starve cells enough to produce diabetes. Lysine may dissolve cholesterol to keep it from clogging veins that could cause heart disease and stroke.[7]

Early versions of APC in clinical tests by Hoffer, Cameron, and Pauling on thousands of cancer patients showed that APC therapy caused no pain or side effects while decreasing the fatigue and pain caused by cancer.[2,5]

APC is available now with some restrictions. IV vitamin C is helpful but not necessary. It may not be available to all patients. Doctors are not permitted to use vitamin C to treat cancer patients.[10] Fortunately, patients can take vitamin C and other vitamins on their own. The political rule of the Food and Drug Administration (FDA) can be avoided if patients start vitamin C and then tell (not ask) their doctors. APC can be used before, during, and after most regular chemotherapies, if necessary. A few types of chemotherapies are not compatible with APC, such as methotrexate and folic acid. Minor but essential vitamins and minerals can be provided by composite pills.

Hoffer's Cancer Treatment

Healthy white blood cells can recognize and kill cancer.[5] Hoffer orally gave vitamins A, B, C, D, E, and other supplements (Table 2). Hoffer offered his multivitamin therapy to an early group of 134 patients who had advanced (even widespread) cancers of many types and who had mostly failed surgery, radiation, and/or chemotherapy. Those who accepted vitamins lived 45 months after seeing Hoffer vs. 2.6 months for the 29 patients who refused vitamins. Table 3 tells how many months patients lived after seeing Hoffer.[5,11] Hoffer thought that one-fourth or half of the doses shown in Table 2 might prevent cancers and possibly many other diseases. Other researchers might choose other supplements and dosages.

Table 3: Survival of Cancer Patients after Seeing Hoffer[5,11]

Type Cancer	With Vitamins	Without Vitamins
Breast	70 months	3.7
Uterus	99	4.0
Ovary	16	3.6
Lung	17	2.0
Pancreas	40	2.4
All 30 types	**45**	**2.6**

Does oral vitamin C kill cancers? Dr. Hugh Riordan showed that oral vitamin C did not raise the blood level of ascorbate enough to kill most cancers.[12]

Most important, Hoffer showed that *oral only* vitamin C, if combined with other vitamins and vitaminlikes, effectively controlled advanced, even metastatic cancers of many types (Table 3).[5]

Regular Chemotherapy

Some of Hoffer's patients took surgery (10%), radiation (16%), or regular chemotherapy (17%) during or after their multivitamins with some taking more than one of these therapies.[5] These therapies may have been taken as "possible insurance." Significantly, over half of his cancer patients did not need regular therapies. His good results (Table 3) suggest that a cancer patient might well use APC for three months to determine if APC is therapeutic so that regular chemotherapy is unnecessary. High-dose vitamin C greatly reduces the side effects of radiation and regular chemotherapy.

What is the Almost Perfect Chemotherapy?

Let me describe APC as strengthening Mother Nature by (1) increasing the dose of compounds that our bodies already use: essential vitamins and minerals plus compounds the body makes: lipoic acid, coenzyme Q10, L-carnitine and lysine and (2) decreasing the intake of compounds that harm the body: hydrogenated fats, sugars, and processed carbohydrates.

The Author's Position

After living 18 years using APC to control my aggressive prostate cancer without surgery, radiation, or chemotherapy and also curing my congestive heart failure, I no longer believe that regular chemotherapy is preferred over APC.[11] Regular cancer therapies should be secondary to multivitamins based on Abram Hoffer's improved multivitamin regimen, as described later.

Vitamin C Functions

Hoffer and Irwin Stone, MD, describe vitamin C as the most important vitamin.[13] Vitamin C is necessary for repair and growth of all tissues.[5,8] Vitamin C helps the immune system by neutralizing free radicals and by fighting infections, colds, cancers, asthma, allergies, and stress, to name a few.[5,13,14] Vitamin C is highly soluble in water. Vitamin C is safe.

With low vitamin C in our blood, heart and leg muscles become weak and white blood cells may no longer recognize and kill germs.[5] Vitamin C regenerates vitamins D and E, lipoic acid, CoQ10, and L-carnitine.[5,8] Vitamin C is especially useful after a stroke or heart attack to repair damaged heart muscles and valves, and damaged parts of the brain that control various functions including memory.[6]

The normal fasting blood level is 0.6 to 1.5 mg/deciliter of ascorbate.[15] A level at or below 0.2 is designated as scurvy. Both scurvy and cancer can cause depression, pain, fatigue, and poor appetite, but doctors rarely check for scurvy.[15,16]

How much vitamin C does a patient need? He or she needs enough to balance all the ills in the body that consume vitamin C. Since many ills

consume vitamin C including cancer, sicknesses, auto accidents, and infected teeth, the dose for a specific patient depends on that patient and his health. Hoffer recommended a dose of 12,000 mg/day for his sick patients, or a dose that almost caused diarrhea.[5] Also, the patient can measure his or her urine for vitamin C level with a purchased dipstick.[15] The urine dipstick should read 50 or 100 mg/dL of ascorbate for good therapy.

With the oral supplements shown in Table 2, the body can kill essentially all types of cancer. IV vitamin C, if it is available, improves APC.[2,5,11]

Vitamin D3 works with vitamin E and calcium to strengthen our bones. It also helps treat cancer, diabetes, cardiovascular diseases, dental health, osteoporosis, muscle strength, and high blood pressure.[17]

Vitamin E is active against aging, cataracts, high blood pressure, and rheumatoid arthritis. It minimizes problems in the lungs, liver, heart, and Alzheimer's disease. Vitamin E is an oil soluble antioxidant that works with vitamin C to repair flesh and bone.[8,18] This combination is especially helpful in repairing small imperfections in the lining of veins. A smooth vein repair prevents the deposition and accumulation of cholesterol and possible subsequent stroke or heart attack.[8,18] Both natural and synthetic forms of vitamin E are available but the natural (d-tocopherols for example) are much more effective than the synthetic (dl-tocopherols).

Coenzyme Q10 (CoQ10) is an antioxidant useful in both wet and fatty tissue. Coenzyme Q10 is a vitaminlike whose production by the body may drop from normal down to only 5% of normal by age 90.[6] It helps with diabetes, general energy, and forgetfulness. There are two types of CoQ10. The common, older version is oxidized and called ubiquinone. It is fat soluble and not well absorbed by the body. It is best taken with peanut butter or other fat, especially by sick or elderly patients.[19] For a group of 13 patients with chronic fatigue, CoQ10 helped 69%.[5] CoQ10 (ubiquinone) can lower systolic blood pressure 16 mm and diastolic 10 mm.[20]

A 69-year-old woman had been taking 400 mg/day of the older type CoQ10 for only a month when she had a severe heart attack. She was given a "vegetative prognosis" but she recovered almost completely in 2 weeks, probably by continuing the CoQ10.[21]

Since 2006 the reduced form of CoQ10, ubiquinol, has been available. This form is more soluble in water, is the form found in human blood, and can be several times more effective than the older type.[20]

Table 4: Statin Effects and CoQ10 Improvement[20]

Problem	Initial%	Final%
Skeletal muscle pain	64	6
Patient fatigue	84	16
Shortness of breath	58	12
Memory loss	8	4
Peripheral neuropathy	10	2

Statins should not be used by cancer or heart patients because they weaken the body and deplete the body of CoQ10.[20] Peter Langsjoen, MD, studied 50 consecutive heart patients who had been taking statins before seeing him. He discontinued the statins and started them on CoQ10 (ubiquinol) for 28 months average. Table 4 shows the problems caused by statins and the improvement when CoQ10 replaced the statins.

Lipoic acid regenerates glutathione and vitamins C and E. It strengthens memory, kills viruses, and helps prevent diabetes.[5] Old rats given CoQ10 and lipoic acid could make four times as much energy in their spinning cages as old rats without supplements.[21] The combination of vitamins C and E, coenzyme Q10, lipoic acid, and glutathione work together to provide energy and healing. Zucker calls them "The Network."[19]

L-carnitine (or acetyl-L-carnitine for brain therapies) helps turn food into energy. It expedites moving fatty acids into muscle cells.[19] The heart prefers to get most of its energy from fats

rather than glucose.[21] When the body uses fat for energy rather than glucose, the body gets 3.5 times as much energy per molecule.[21] L-carnitine provides energy for walking and for recovering strength after a heart attack or stroke. L-carnitine with lipoic acid helps to improve memory.[6]

Stress

Stress of any kind can precipitously lower the vitamin C in the body, even to one fourth its previous level.[13] Stroke and cancer can cause stress and often scurvy.[5] Vitamin C helps combat stress, whatever its cause. Most animals under sudden stress produce more vitamin C. Stress from surgery, or a fall may cause scurvy, often 5 or 10 hours after the incident. We can measure our blood ascorbate with a urine dipstick and take more vitamin C as needed.[15] ➤

The supplements mentioned here often make a big improvement in how well we feel.[5,19] Supplements work best if taken along with a good lifestyle and regular exercise.

Specific Diseases

Stroke and Heart Diseases are too dangerous and difficult to treat without the help of a suitable doctor. However the therapy for the Almost Perfect Chemotherapy may be similar to that for stroke and heart disease, Table 5. As noted later, the author used a simpler therapy to recover from congestive heart failure.

Table 5: Atherosclerosis and Congestive Heart Failure, Stages I and II[21]

	Daily doses
Lecithin	15–30 grams
Vitamin B-3	1000–3000 mg
Chromium	200–400 mcg
Magnesium	300–600 mg
Vitamin E natural,	200–1600 IU
Vitamin B-6	75 mg
Vitamin D-3	5000 IU
CoQ10, ubiquinone	300–600 mg
Lysine, mg	2000 or more
Vitamin C, mg	2000–6000+

Diet: More omega-3 fatty acid. Less processed carbohydrates & sugars. Less hydrogenated fats.

Common Cold and Viral Diseases: The common cold is a miserable virus. Modern medicine has no good medicine to fight viruses. Alternative medicine practitioners use vitamin C to easily kill viruses.[2,22] Pauling and Cathcart successfully controlled colds by giving 1000 mg of vitamin C each hour as long as cold symptoms were present.[2,22] The regimen is quite flexible.[13,14]

Dr. Frederick Klenner reported that all viruses can be cured by sufficient vitamin C given repeatedly at short time intervals.[14] He cured 60 out of 60 cases of poliomyelitis in a week or two by giving up to 210 grams of IV vitamin C daily depending on the weight of the patient. He also treated 8 shingles patients with injections of sodium ascorbate. Pain ceased in 2 hours after the first injection and lesions cleared in 3 days.[14]

What about the viruses of influenza, bronchitis and viral pneumonia? Klenner treated viral pneumonia with 1 gram of IV sodium ascorbate every 6 to 12 hours plus oral ascorbic acid at 100 to 500 mg every 4 to 6 hours.[14] Patients felt better 1 hour after the first IV, and their temperature dropped 2 °F after several hours. Unfortunately, doctors seem to avoid vitamin C for treating viruses.

Diabetes and Alzheimer's disease: Semipermeable membranes surround all the cells in our bodies. These membranes control the flow of food and other materials into and out of the cells. When, over the years, we have eaten too much hydrogenated fat, the membranes may become less permeable and defective.[9,23] Sugars cannot properly enter defective cells even when aided by insulin. This may cause the cells to have insufficient energy. Type 2 diabetes may result if the cells affected are in the heart, eyes, or legs.

Diabetes type 2 may be corrected slowly (in months) by a diet low in sugars and hydrogenated fats but high in vitamin C and omega-3 fatty acids.[8,23] Fish and fish oil pills are good sources of omega-3-fatty acids.

Some think that Alzheimer's and/or Parkinson's diseases are type 3 diabetes since the cells affected are brain cells.[24] Treating brain disease is agonizingly slow and without accepted therapies. Present drugs aim to slow the diseases for months or perhaps a year. They offer little hope of improving memory. Much work has been done on Alzheimer's disease but no accepted therapy exists. We will consider one of many suggested therapies: acetyl-L-carnitine. Acetyl-L-carnitine has shown some signs of improving memory. The Mini Mental State Examination (MMSE) is one of several commonly used tests to measure memory. L-carnitine was used to treat a randomized, double-blind group of 66 centenarians.[25] Half were given 2 grams/day of L-carnitine for 6 months and their MMSE increased from 16.4 to 20.5 with 30 being the maximum. The placebo group had an MMSE score that changed insignificantly from 16.6 to 17.2. An MMSE gain of 4.1 for patients is a huge help. Acetyl-L-carnitine was tested on several groups of somewhat younger patients with variable results.[25]

Safety

Dr. Hugh Riordan suggested the precautions shown in Table 6.[11] Many patients have safely taken vitamin C at doses of 40,000 mg/day and even larger. Hunninghake found very few cancer patients who could not take vitamin C because of their deficiency of G6PD. However, Cameron and Hoffer used mostly oral vitamin C and did not report that they checked G6PD. They both found that oral vitamin C easily killed cancers.

Table 6: Precautions with High-Dose Vitamin C[12]

1. Build up the dose slowly by about 1000 or 2000 mg/day to minimize diarrhea.
2. If necessary, decrease the dose slowly to allow the body to adjust.
3. Vitamin C in the form of ascorbic acid pills may cause gas, upset stomach, or skin itch. If this occurs, consider using powdered vitamin C or capsules that are less upsetting than pills with binder.
4. Excess sodium intake from sodium ascorbate is possible. Consider using ascorbic acid or a mixture of sodium ascorbate and ascorbic acid.
5. Some people lack the glucose-6-phosphate dehydrogenase (G6PD) enzyme. Patients considering IV vitamin C should be tested for this. These people may not be able to take IV vitamin C without getting hazardous acute anemia.
6. For their own safety people should work with a doctor knowledgeable about vitamins.
7. All people may not be able to use high doses of vitamin C.

Prevention

Hoffer suggested that the vitamins that he chose (Table 2) if taken at reduced amounts might help prevent cancer and other diseases.[5] Instead of starting with a handful of pills, may I suggest starting with vitamin C at 1000 mg, natural vitamin E at 400 IU, and ubiquinol (CoQ10) at 100 mg for both breakfast and dinner? This makes three pills taken twice a day. This short regimen is untested.

Pain Control

For some patients, pain is worse than death. Narcotic type drugs are often a wonderful aid, but unfortunately they cannot always control the pain. The pain from cancer (and other sources) is directed to the opiate receptors in the brain, according to Drs. Alfred Libby and Irwin Stone.[26] High-dose vitamin C is also absorbed in the opiate receptors where it can displace the narcotic drug and thus block the pain. The opiate receptors may have become part of our brains thousands of years ago to preserve vitamin C in the body when vitamin C was in short supply.

Ewan Cameron gave his advanced cancer patients large doses of vitamin C to treat their cancer. To control the pain of cancer eating bone, he also administered large doses of narcotics as needed. Five of his first such patients found that their pain almost disappeared and they no longer asked for narcotics.[2] They had no side effects from stopping the narcotics! Cameron typically gave 10 grams (10,000 mg) per day.

Libby, a family doctor, treated street drug addicts with 25 to 80 grams (2.3 to 8 tablespoons) per day of sodium ascorbate powder dissolved in milk. One incoherent patient became coherent in 45 minutes after consuming 30 grams of ascorbate.[26] Andrew Saul had a very sick cancer patient who took about 100 grams per day of vitamin C dissolved in water. He improved from painfully bedridden to walking some in the yard.[27]

Patients with uncontrolled pain from cancer might consider trying high-dose vitamin C such as 25 grams of sodium ascorbate in milk or water. This is taken throughout the day. Loose bowels or diarrhea could indicate the proper dose. If no pain relief or loose bowls result, the daily dose can be increased even to 100 grams a day. After a day or two, the dose should be reduced to avoid diarrhea. I recommend that patients work with their doctors for safety and to keep electrolytes and nutrition in balance.

Author's History

At age 73, I felt healthy. At age 74, I knew I had aggressive prostate cancer. I refused radiation and chose temporary hormone therapy. A few months later I started Hoffer's multivitamin regimen. At age 87, I was diagnosed with congestive heart failure and given a pacemaker and diuretics. With Hoffer's regimen, I have kept my aggressive prostate cancer in remission for 18 years. As of May 2015 at age 92, my PSA was a healthy 1.5. I have recovered from congestive heart failure probably by adding lipoic acid and acetyl-L-carnitine to Hoffer's multivitamins.

Vitamins, diet, exercise, the love of God, and lifestyle have controlled my cancer and heart diseases.

My daily exercise usually includes walking up three floors of stairs in a moderate 50 seconds. My parents both died of cancer in their mid 60s, so their genes may have contributed to my cancer but not to a short life for me.

Discussion

To use vitamins as cancer therapy is a new and difficult thought for many doctors and patients. The pharmaceutical industry has successfully belittled vitamins for many decades. Fortunately the evidence for multivitamins properly administered for cancer therapy is excellent and convincing. The Almost Perfect Chemotherapy works without bad side effects. Regular chemotherapy is widely used but has a poor reputation.

The FDA controls the use by doctors of many supplements. Doctors will often go along with patients who have already started vitamins.[10,11,28] A doctor who prefers to offer APC could offer a cancer patient surgery, radiation, and chemotherapy. If patient refuses each regular therapy, the doctor could then offer vitamin therapy and make a note in the patient's record to answer the FDA. A patient can tell the doctor that he will not accept surgery, radiation, or chemotherapy and would the doctor assist with vitamin therapy? The author did this. All of his doctors have cooperated

Few doctors use CoQ10, lipoic acid, or L-carnitine even when allowed. The big drug companies do not advertise these economical, nonpatentable items. Fortunately cancer patients can take vitamins on their own choice without restriction from the FDA. ➤

➤

Although developed for cancer treatment, APC strengthens the immune system and may help generate energy throughout the body.

Importantly, a strong immune system may control stroke, cardiovascular diseases, and many other sicknesses.[5,6,21]

When people and patients learn that economical, safe, over the counter supplements may control many diseases, people may live longer with less pain, less cost, and fewer side effects.[5,28] Sick patients who choose vitamins can expect positive results often in a month.[28] If a person feels sick or the doctor does not yet have a diagnosis, the patient might well consider strengthening his immune system with the Almost Perfect Chemotherapy, preferably with the knowledge of the doctor.

Dr. Herbert Newbold found that his patients who were in moderately good health when the time came to die, died more quickly and with less pain.[29]

A strong immune system may cut colds and other diseases in half and avoid expensive hospital visits.[2,22,28] Doctors and hospitals using today's expensive medicine will often resist change and they will argue against vitamins for cancer and other diseases. However patients have the power and the money.

Summary

The Almost Perfect Chemotherapy strengthens Mother Nature by (1) increasing the dose of compounds that our bodies already use: essential vitamins and minerals plus compounds the body already makes: lipoic acid, coenzyme Q10, L-carnitine, and lysine and (2) decreasing the intake of compounds that harm the body: hydrogenated fats, sugars, and processed carbohydrates.

Oral vitamins working together have controlled many types of cancer at all stages. IV vitamin C is not necessary but is helpful if available.[12]

The cost of APC is far less than surgery, radiation, or chemotherapy.[10] Although vitamins can be chosen and used by healthy or sick people, professional supervision is often helpful.

If enough people on their own strengthen their bodies by multivitamins, our general health might greatly improve.

Can we greatly cut the cost of stroke, cancer, and heart therapies? Can we cut colds and sick days significantly?[2,5,6,8,14] I believe that we can.

Conclusions

1. The APC consists of vitamin C augmented by other vitamins, essential minerals, and four vitaminlike items made by our bodies: coenzyme Q10, lipoic acid, acetyl-L-carnitine, and lysine. A diet including omega-3 fatty acids and fewer hydrogenated fats and carbohydrates may be necessary.
2. The APC was used by Dr. Abram Hoffer to treat a group of 133 advanced cancer patients of many types who had mostly failed regular therapies. Those who accepted APC lived 45 months with less pain and side effects, while the 29 who refused APC lived only 2.6 months after seeing Hoffer.
3. APC has clinically treated over 1000 cancer patients, often with results better than standard chemotherapy and without side effects.
4. APC has strengthened the immune system to help control various diseases including cancer, stroke, heart diseases, scurvy, and the common cold.
5. APC is available now if patients choose to start APC. The FDA does not restrict patients from using APC, although guidance by appropriate doctors or health professionals is recommended.

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The P53 Tumor Suppressor Gene: Understanding P53-Based Anticancer Therapies Utilizing Dietary Agents

by Serge Jurasunas, ND, MD (Hom)

Abstract

The P53 tumor suppressor gene, which has been dubbed both the "Guardian of the Genome" (Lane 1992) and *Science* "Molecule of the Year," is directly involved in the initiation of apoptosis and programmed cell death, to prevent an accumulation of abnormal cells. However, apoptosis evasion is a characteristic feature of human cancers that promote tumor formation and progression.[1] Presently, P53 is known to play a key role in practically all types of human cancers, and the mutation or loss of P53 gene function can be identified in more than 50% of all human cancer cases worldwide.[2]

Frequency of P53 Mutations

70% in lung cancer

60% in cancers of colon, head, neck, ovary, bladder

45% in stomach cancer

35%–40% in breast cancer

Recent data have shown that, in addition to losing transcriptional function, mutant P53 gains oncogenic functions termed GOF (gain of function) that drive cell migration, invasion, and metastases.[3,4] The notion for mutant P53 GOF theory is supported by recent studies using mutated P53-blocked mice which display a broader tumor spectrum, increased aggressiveness and metastatic potential as compared with their P53-null counterparts.[5,6] Similarly, in human cancers mutant P53 expression has been linked with a poor prognosis.[7] Therefore, mutant P53 function raises the possibility that the mutant protein may be a good target for designing novel therapies.

The P53 pathway seems to play a critical role in therapeutic response both as a diagnostic and marker in the prognosis of therapeutic treatment effects.

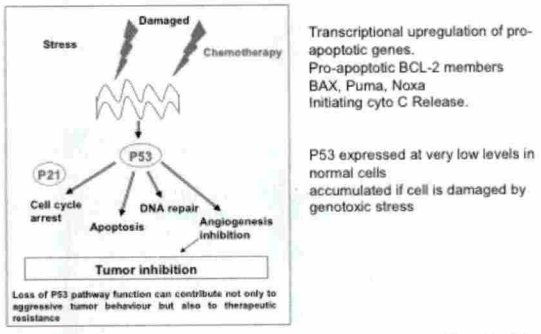
The inability of most cancers to undergo apoptosis in response to appropriate stimuli is a key cause of treatment failure, presenting one of the major yet unsolved problems in oncology.[8]

Introduction

Programmed cell death, called apoptosis, is a fundamentally important process that prevents an accumulation of genetically abnormal cells. Apoptosis induction often appears to be related to the production process of P53 protein. This follows the activation of the tumor suppressor gene as a stress response to any DNA damage within a cell nucleus.[9] In normal, unstressed cells, P53 is expressed at a very low level; the half-life of the protein does not exceed 20 minutes.

Active P53 binds to target DNA and determines the choice between triggering cell cycle arrests at a checkpoint to allow DNA repair or activating a special molecular pathway leading to the self-destruction of a cell through apoptosis. Both alternatives provide any organism with genetic stability.

Table 1



Oren M. (2003) decision making by P53 – Life, death and cancer – Cell death Differ 10 – 431-442

The critical role of P53 is made evident by the fact that it is mutated in approximately 50% to 70% of all human cancers. In fact, P53 is the most commonly mutated gene in human cancer. In human malignancies, very often there are ➤

mutations or a loss of alleles in the gene located on the chromosome 17P. More than 500 mutations in the P53 gene have been discovered, although they are not equal in terms of biological activity.

The mutated gene in transformed cells leads to protein confirmation changes and the accumulation of very stable mutant forms of P53 in the nucleus. All types of mutated P53 are likely to be ineffective in maintaining a nontumorigenic cellular phenotype when compared with a wild-type P53.

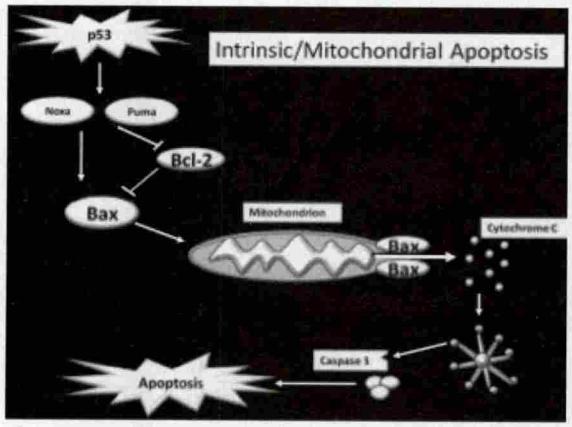
Wild-type P53, a nuclear phosphoprotein, has been shown to be a sequence specific transcription factor which induces the expression of P21, WAF1/C1P1/Sdi-1, leading to a G1 arrest checkpoint to step up repair before DNA replication and contributes to normal cell proliferation; unless DNA replication is successful, the cells will be induced to undergo apoptosis.[10]

However, during a stress response from its P53 gene to any damage, recent findings suggest that P53 induces apoptosis by transactivating expression of the BAX gene mRNA to increase BAX protein and simultaneously inhibit the function of Bcl-2.[11] RNA proteins are homologs, though BAX acts as an accelerator of apoptosis while Bcl-2 serves to prolong survival.[12]

This suggests that P53 mutation not only serves to inactivate the proapoptotic P53 pathway but may also play an additional role in tumor progression. Mutant P53 itself provides a selective advantage to tumor cells and promotes tumor growth. Recent data suggest that expression of mutant P53 is not the equivalent of P53 loss, wherein mutant P53 can acquire new functions.

Bcl-2 activity upregulates in many types of cancer and correlates with cancer cell resistance to a wide spectrum of chemotherapy agents.[13] Overexpression of the antiapoptotic Bcl-2 proteins blocks cytochrome C release in mitochondria in response to a variety of stimuli, whereas the proapoptotic BAX protein releases cytochrome C that in turn activates an apoptotic cascade, while the loss of BAX is associated with tumor progression and shorter survival in metastatic breast cancer.[14]

Figure 2



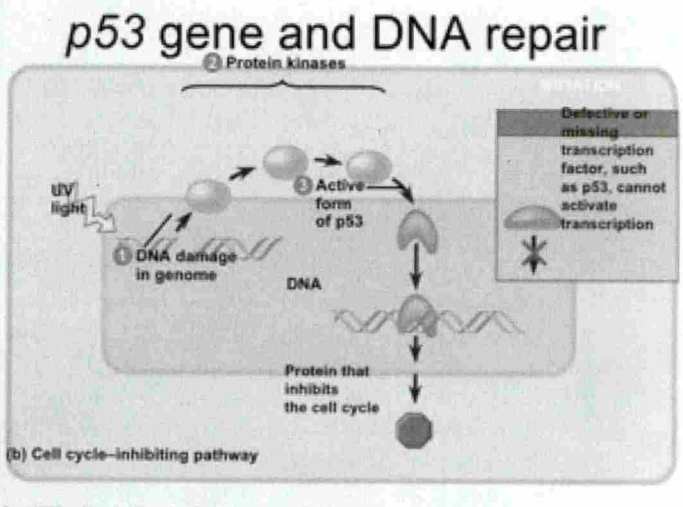
BAX was the first identified P53-regulated, proapoptotic Bcl-2 family member. P53-responsive elements have been unequivocally identified in the BAX gene.[15] BAX is specifically required for PUMA (p53-upregulated modulator of apoptosis)-mediated apoptosis, and it also participates in the death response as an indirect target of P53 through PUMA and Noxa, both implicated in P53-dependent apoptosis.[16]

Some studies show that the loss of BAX is responsible for nearly half of the accelerated tumor growth in brain tumors that are related to loss of P53 function.[17] BAX is inactive in approximately one-third of invasive breast cancers; in a study of 119 women with metastatic breast cancer, it was found that patients whose tumors had lost BAX activity had poor responses to combination chemotherapy, faster time to tumor progression, and shorter overall survival.[18]

This may suggest that turning on this proapoptotic gene may be important for chemotherapy response, wherein one of the factors that can regulate BAX gene activity is the P53 tumor suppressor gene, which also simultaneously inhibits Bcl-2 during the process of apoptosis. Nevertheless because BAX proteins antagonize Bcl-2 antiapoptotic function, it is likely that the Bcl-2/BAX balance ratio determines both the susceptibility of a cell to apoptosis and therapeutic response to apoptosis stimuli.[19]

If apoptosis signaling is not initiated by nuclear P53 and/or the presence of a mutated P53 gene, loss of BAX, and overexpressed Bcl-2, this allows some cancer cells to divide unchecked after radiation or chemotherapy treatment, associated with cancer cell resistance, increased rate of tumor recurrence, and shorter patient survival.[20]

Figure 3



Another profound feature of malignant cells is their ability to induce angiogenesis necessary for tumor growth. Again, there is a clear correlation between mutant P53 GOF that facilitates angiogenesis by increasing the expression of VEGF, via interaction with E2F1 that induces the expression of ID4, which in turn promotes the expression of proangiogenic factors such as IL and GROa, thus

eventually leading to increasing angiogenesis in cancerous tissues.[21,22] Other novel functions of mutant P53 GOF are shown through the activation of specific target genes EGFR/1, RAS, Myc, and interference with the TGFB growth arrest control pathway, downregulation of the E-cadherin cell-cell adhesion molecules to enhance motility, and tumor cell migration and invasion.[23]

We have new clues and important conceptualizations which indicate that tumors cannot be viewed simply as an uncontrolled proliferative mass, but rather as a cellular community, interacting with a microenvironment.[24,25] This is why targeting mutant P53 remains an urgent need to improve cancer treatment by increasing a cancer cell's sensitivity to apoptosis.

Therapeutic Strategy

Targeting mutant P53 and restoring the wild-type function of P53 tumor suppressor gene in tumor cells would be of potential therapeutic benefit and an attractive strategy for anticancer treatments.[26,27] Upon restoration of P53 transcriptional activity, the apoptosis pathway would predominate.

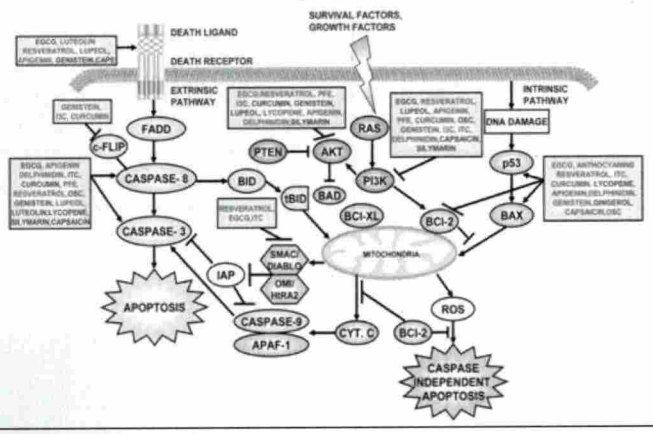
Many cancer cells escape apoptosis and become resistant to chemotherapy radiation or from destruction by the immune cells by endogenous cytotoxic T-cells and natural killer (NK) cells. If the oncogene Bcl-2 is highly expressed it confers greater resistance to cancer cells from attacking immune cells, increasing the urgent need for effective cancer therapies.

Furthermore, some of the P53 apoptosis targets such as BAX, PUMA, Noxa, and P21 could potentially be used as targets for gene therapy to increase the effectiveness of chemotherapy.

Dietary Agents that Induce Apoptosis with Chemo Preventive Effects

A large number of dietary agents can exert effects on the human genome either directly or indirectly to modulate gene expression. Extensive research during the last half-century demonstrated that numerous agents identified from fruits and vegetables can interfere with several signaling pathways and were validated as apoptosis inducers in research experiments.

Figure 4



P53 Tumor Suppressor Gene

These dietary agents include well-known, well-documented substances recommended for cancer prevention and therapy, such as curcumin (turmeric), resveratrol (grapes), genistein (soybean), capsaicin (red chili), ellagic acid (pomegranate), caffeic acid and phenyl ester (propolis), polyphenols (green tea), catechin (green tea), and indole-3-carbinol (cruciferous vegetables).[28–36]

They have all clearly accumulated evidence demonstrating their efficacy to induce apoptosis by modulation of the P53 independent pathway, BAX, BAK, targeting the antiapoptotic proteins, Bcl-2, and survivin gene so as to potentialize a chemotherapy/radiation regimen. Curcumin, for instance, has been found to inhibit the activity of NF-kB and Bcl-2, and increase P53 activity as well as sensitize cancer cells to cisplatin- and Taxol-induced apoptosis.[37] The combination of 5-Fu and genistein enhances therapeutic effects in colon cancer through the COX-2 pathway.[38] Genistein combined with docetaxel or gemcitabine significantly inhibited Bcl-2/Bcl-xL, survivin, and induced P21 WAF1, suggesting that combination treatment regulates the important molecules in the apoptotic pathway.[39,40] Green tea and black tea cause induction of apoptosis accompanied with upregulation in BAX and a decrease in Bcl-2 proteins in prostate cancer cells.[41] Capsaicin-caused apoptosis in prostate cancer cells shows an increase of P53, P21, and BAX.[42] Curcumin downregulates the apoptosis suppressor proteins Bcl-2 and Bcl-xL in several cancer cell lines, thus increasing apoptosis overall.[43]

In human breast cancer cells, curcumin induces apoptosis through P53-dependent BAX induction; curcumin, resveratrol, and green tea polyphenols are also known to downregulate the expression of apoptosis suppressor proteins such as Bcl-2 and Bcl-X in several cancer cell lines.[44]

In human prostate carcinoma LNCaP cells, treatment with EGCG-induced apoptosis was associated with stabilization of P53, with an accompanying downregulation of NF-kB activity resulting in a decreased expression of the antiapoptotic Bcl-2. Overall dietary agents synergize with chemotherapeutic drugs, thereby reducing the toxicity of chemotherapeutic agents.[45]

Numerous studies continue to report that resveratrol exerts its anticancer effects by causing cell cycle arrest and inducing apoptosis in many different cancers.[46] These include colon adenocarcinoma cells (Caco-2), esophageal carcinoma cells, medulloblastoma cells, the highly invasive and metastatic breast cancer cell line MDA-MB-231, melanoma cells, pancreatic carcinoma cells, esophageal squamous carcinoma cells, and lung cancer cells.

A complete document concerning the modulation of apoptosis by active compounds for cancer therapy and their synergy with chemotherapeutic agent is available at www.sergejurasunas.com.

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Conclusion

Deregulation of P53 has enormous influence on carcinogenesis as mutant P53, which can induce an increased epigenetic instability of tumor cells, facilitating and accelerating tumor evolution.

An increasing body of investigation has shown that inhibitor of apoptosis protein (IAPs) as Bcl-2, survivin, and so on, is now seen as diagnostic markers for early-stage malignancy and novel prognostic markers.[47] In addition these molecules have been validated as therapeutic targets. Accumulated evidence clearly indicates that dietary agents may play a critical role by targeting P53 and IAPs and improve chemotherapy regimen. Despite significant

Table 1: Effects of PSJ-53 Therapy on the Tumor Suppressor P53 Pathway

M: Case of Multiple Cancer Recurrence

		P53 protein level units/ml of plasma			
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * <10^6 copies/ml of plasma	Comments
1	2 Feb 2009	ND**	26.1	2.7×10^5	The blood sample was collected prior to PSJ-53 therapy
2	18 May 2009	16.8	ND**	8.9×10^{11}	The blood sample was collected after a 3 month course of PSJ-53 therapy
3	21 Sep 2009	156.0	ND**	1.5×10^{13}	The blood sample was collected 4 months after completion of the PSJ-53 therapy during which time no further treatment was given

Table 2: F: 48 Years Old: Breast Cancer – Breast Cancer in Remission 2009

		P53 protein level units/ml of plasma			
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * <10^6 copies/ml of plasma	Comments
1	2 Feb 2010	ND**	52.5	52.245	The blood sample was collected prior to PSJ-53 therapy
2	19 Apr 2010	10.99	ND**	170.000	The blood sample was collected after a 2 month after completion of the PSJ-53 therapy

The results clearly show the presence of mutated P53 prior to PSJ-53 therapy. However, after 2 months of the treatment, we reversed the mutant P53 to a normal wild-type function, associated with an increase of the P53 gene expression and protein level during this period of time.

Table 3: F: 56 Years Old – Pancreatic Cancer – 5 Years of Remission

		P53 protein level units/ml of plasma			
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * <10^6 copies/ml of plasma	Comment
1	4 May 2009	ND**	52.5	52.245	The blood sample was collected prior to PSJ-53 therapy
2	4 July 2009	10.99	ND**	170.000	The blood sample was collected after a 2 month after completion of the PSJ-53 therapy
3	17 Nov 2009	67.4	ND**	1.2×10^6	The blood sample was collected after a 4 month after completion of the PSJ-53 therapy

The results clearly show the presence of mutated P53 prior to the PSJ-53 therapy. However, after 2 months of therapy followed by 4 months of treatment, we reversed the mutant P53 to a normal wild-type function, and gradually the P53 wild protein production rose to a high level, leading to increased self-destruction of cancer cells.

advances in cancer diagnosis and therapy, there is still little progress in the treatment of advanced disease.

Most modern medicines currently available for treating cancer are very expensive, toxic, and less effective in treating the disease. Therefore new effective ways to treat cancer have become a priority. Thus, one must investigate further in detail, dietary agents derived from natural sources without toxicity. Hopefully, they will find a place in the clinical management of patients with malignancy.

Case Reports

We have been measuring the activity of P53 pathway, BAX, Bcl-2, survivin, and P21 gene expression with a large number, variety, and grades of cancer patients, developing a targeting therapy that could restore mutant P53 to a normal wild-type function as a first step after gaining results to modulate BAX, inhibit the Bcl-2 and survivin antiapoptotic proteins. The targeting therapy includes dietary agents such as curcumin and other compounds empirically experimented upon by the author. It includes an extract of fish oils rich in oligopeptide, that contain short-chain amino acids shown to have efficiency to target mutant P53, fermented chlorella in tablets rich in vitamins, minerals, and nucleic acids.[48] The fermenting process increases the level of nutrients and absorptive power. Finally, an antioxidant compound was derived from modified vegetables and seeds, with low molecular weight having SOD-like activity.[49]

This targeting therapy, known as PSJ-53 therapy, had been first utilized in experiments to restore mutant P53 and proved by P53 gene expression and P53 protein testing. Later experiments in modulating BAX gene expression and ➤

Table 4: M: 81 Years Old: Recurrence of Colon Cancer – Liver Metastases

The patient refused chemotherapy but agreed to take some radiation therapy. He was sent by his medical doctor to take molecular markers testing to first check whether radiotherapy would be efficient. P53, BAX, or P21 should be active and sensitive to radiation, and increase self-destruction of cancer cells.

New Reference range: P53 protein level wild – 0.10 – 1.00 units/ml of plasma

P53 gene expression: .....10-50 units/ml of plasma
Bcl-2 gene expression:.....10 units
BAX gene expression: .....10–100 units
Survivin gene expression: .....10 units
P21 gene expression:.....10–50 units

		P53 protein level units/ml of plasma						
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * $<10^6$ copies/ml of plasma	Bcl-2	BAX	Survivin	P21
1	1 Mar 2011	ND**	10.88	ND**	390	ND**	129	ND**
2	11Jul 2011	ND**	ND**	1.180	ND**	409	ND**	ND**

The results clearly show after 4 months of treatment a significant improvement and reversal of the mutant P-53 tumor suppressor gene. However, the P53 gene didn't induce the level of normal protein (often because of a blockage of PUMA). BAX gene expression is now active as a pathway to destroy cancer cells and the oncogene Bcl-2 and survivin are not active due to the applied treatment. Therefore the new pattern showed that cancer cells were destroyed and that radiotherapy would be efficient, increasing the destruction of cancer cells. The first report showed Bcl-2 and survivin were slightly active (at risk) but after the treatment were totally inhibited, which contributed to increase the efficiency of chemotherapy/radiation regimen. After radiation therapy and further treatment with natural compounds, the patient was free from liver metastases.

Table 5: M: 50 Years Old – Lung Cancer

		P53 protein level units/ml of plasma						
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * $<10^6$ copies/ml of plasma	Bcl-2	BAX	Survivin	P21
1	7 Jan 2013	ND**	16.26	ND**	340	330	1.028	552
2	11 Mar 2013	0.1	ND**	3	2	5	5	4.527

Ratio of the 1st Analysis
Bcl/BAX: 0.89
Survivin/P21:0.53
Ratio of the 2nd Analysis
Bcl/BAX: 2.5
Survivin/P21: 905.4 – too high to make a ratio

The results clearly show after 2 months with PSJ-53 therapy that we reversed mutant P53 to a wild type function, but P53 protein was produced only to a certain extent. However, we have targeted Bcl-2 and especially the high expression of survivin to a normal range and eliminated resistance in some population of cancer cells and increased the self-destruction of cancer cells through chemotherapy/radiation with a resultant decrease in lung nodule size. P21 gene expression is very highly active (4.527) and promotes the self-destruction of cancer cells. P21 is a P53-independent channel to apoptosis and can be independent of P53 activated by another channel such as the TGF-B. P21 is very sensitive to radiation in destroying cancer cells.

targeting Bcl-2 and survivin antiapoptotic proteins were shown to potentialize the efficiency of chemotherapy and radiation.[50] Survivin, a unique member of the IAPs, inhibits caspase-7 and -9 and promotes both cell proliferation and angiogenesis.[51] Measuring and targeting survivin remains a major goal in response to antineoplastic agents.[52]

We present three cancer cases with blood analysis reports of P53 gene expression and mutated protein levels before and after the treatment, along with two cases with complete figures of the proapoptotic and antiapoptotic genes before and after treatment.

1. a case of multicancer recurrence.
2. remission of breast cancer
3. pancreatic cancer
4. recurrence of colon cancer
5. lung cancer
6. glioma

Methodology

P53 pathway activity and other proapoptotic and antiapoptotic genes were evaluated by measuring protein concentration and the level of P53 gene expression, Bcl-2, BAX, survivin, and P21 in the same peripheral venous blood obtained from patients in the clinic.

The enzyme-link immunosorbent assay (ELISA) was used together with the polymer chain reaction (PCR) to evaluate P53, BAX, survivin, and P21 gene expression levels and for the qualitative detection of P53 protein. Blood samples were collected in sterile tubes and sent to a laboratory specializing in molecular marker tests, which offers complete reports and discussion about each test.
Survivin/P21: 0.53

We have clearly demonstrated that mutant P53 can be targeted together with other proapoptotic and antiapoptotic genes using dietary compounds, which for many patients has been proved with many scientific examples. This is only one example and not the publication of cancer cases followed over a 1- or 2-year period as we have done with many patients. This child has now been treated for over 2 years with excellent results, and has taken 5 blood analyses, which each time indicated what treatment should be done. However, my last article in the *Townsend Letter* 2014 showed complete cases relative to breast cancer with molecular marker testing done over a 1-year period and more. Step by step it showed improvement and the normal balance between the proapoptotic and antiapoptotic genes.[50]

New avenues are now focusing on targeting apoptosis in cancer, which include oncogenes, Bcl-2, and survivin that increases cancer cell resistance to chemotherapy/radiation regimen, while scientific literature today has already accumulated thousands of articles on laboratory reports, theories, and studies.

We urgently need to put into clinical practice what we have discovered and learned. Targeting P53 and other genes remain one of the greatest challenges in the treatment of cancer. We have been working now for over 8 years with molecular markers as a diagnostic, prognosis, and follow up to treatment, selected the appropriate bioactive dietary compounds or anticancer agents, exceeding 1000 cases, blood tests, and successes. This may be an incentive for more doctors to venture into this new direction in order to achieve more beneficial results with patient treatment, especially in cases where we can verify the ones who would be refractory to chemotherapy and have a poor response. It is always best to first check through patient testing, to determine whether or not chemotherapy would be beneficial.

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Table 6: F: 8 Years Old – Glioma
Postponed chemotherapy after three surgeries and poor results.

		P53 protein level units/ml of plasma						
No	Date of blood sample collection	Wild P53 Ref. range* <0.33 units/ml of plasma	Mutated P53 Ref. range ND**	P53 gene (wild expression level Ref. range * $<10^6$ copies/ml of plasma	Bcl-2	BAX	Survivin	P21
1	6 Jan 2013	0.2	ND**	1.344	2.066	1.714	1.734	2.192
2	11 Mar 2013	16.4	ND**	820	131	ND**	ND**	229

shorter survival in women with metastatic breast adenocarcinoma. *Cancer Res.* 1995;55:4471–4478.
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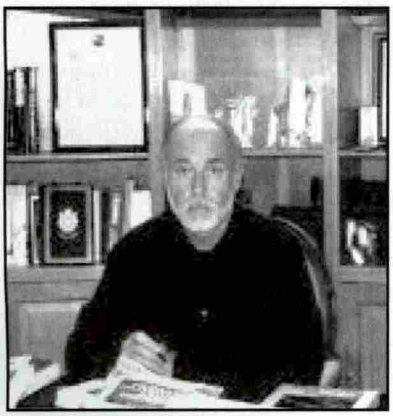
Professor Serge Jurasunas, a frequent *Townsend Letter* contributor, will be the featured speaker at the Physician's Round Table Conference to be held in Tampa, Florida, January 29–31, 2016, together with other well-known integrative cancer doctors. He will present two lectures: "Health and Disease Begin in the Colon, As Seen through Iridology" (he will be signing his new expanded book on the subject), and "How to Understand Cancer from a Molecular Basis." He will show how cancer can be diagnosed earlier on and then treated with dietary agents.

For additional information, contact Peerobmagazine@aol.com.



Serge Jurasunas is an internationally well-known doctor of naturopathy and alternative medicine with over 40 years of experience in the treatment of cancer. He is developing innovative therapies in cancer treatment and is a pioneer in live blood analysis, dried blood oxidative stress, and iridology.

Dr. Jurasunas is busy working with P53 tumor suppressor gene and other molecular markers testing related to cancer patients and patients with high risk of cancer.

For more information and to learn about cancer treatment, molecular markers, and clinical cases at Holiterapias Clinic, please visit www.sergejuraunas.com; e-mail: info@sergejurasunas.com; phone: +351 213471117.

Acidity Kills the Pancreas

by Peter Melamed, PhD, and Felix Melamed, MS

Abstract

Three main, interrelated reasons for widespread digestive disorders in the modern world might be chronic metabolic acidosis, low exocrine pancreatic function, and intestinal dysbiosis. Chronic metabolic acidosis mainly distresses two alkaline digestive glands: the liver and pancreas, which secrete alkaline bile and pancreatic juice with a great amount of bicarbonate. The acidic shift in the bile and pancreatic juice pH can cause serious biochemical/biomechanical problems. The pancreatic digestive enzymes need an alkaline milieu to function properly; therefore, low pH disables their activity. This may be the crucial cause of indigestion. Acidification of the pancreatic juice decreases its antimicrobial activity, promoting intestinal dysbiosis. Reducing the pH of the pancreatic juice can lead to the premature activation of the proteolytic enzymes inside the pancreas, potentially leading to pancreatitis. The acidification of bile produces bile stone formation and precipitates aggressive bile acids, which irritate the entire biliary system. An aggressive combination of the acidic bile and the pancreatic juice can activate irregular spasms of the duodenum's walls and consequent bile reflux into the stomach and the esophagus. The normality of the exocrine pancreatic function is the core of proper digestion. Presently, there is no efficient and safe treatment for enhancing exocrine pancreatic function. Reinstating normal acid-base homeostasis can be a pathophysiological therapeutic approach for numerous gastrointestinal disorders. There is strong scientific research and practical evidence that restoring the $HCO3^-$ capacity in the blood can improve digestion.

Introduction

The interrelated combination of chronic metabolic acidosis, low exocrine pancreatic function, and intestinal dysbiosis can explain the widespread digestive disorders in the modern world. Altogether, these causes create a vicious circle.[1] There is not enough time for genetics to be implicated in these disorders; therefore, many scientists and doctors pay attention to environmental factors, such as food, water, stress, lifestyles, toxic chemicals, alcohol consumption, and the inner ecology.

The acid-base balance, or acidity/alkalinity balance, is a critical factor in the health and functioning of the body. Optimal health depends on the body's ability to maintain a slightly alkaline state.

Pathophysiology of Metabolic Acidosis

Normally, blood is slightly alkaline, with a pH range of 7.35 to 7.45. The consistency of the blood pH is essential to the body's ability to maintain a relatively stable internal environment. Its importance is demonstrated by the fact that a human being cannot live if the blood's pH goes below 7.0 or above 8.0. For example, blood with a pH of 6.95, which is only slightly acidic, can lead to coma and death.

Many body functions are designed to control the acid-base balance, including respiration, digestion, circulation, excretion, and cellular metabolism. The acid-alkaline regulation systems are interrelated and work together to prevent acute or chronic changes in the body's acid-base balance.

What causes the body to be too acidic? The main persistent factors are:

- The creation of too many acidic materials by human cells. For instance, the end products of cellular metabolism are amino acids, fatty acids, carbonic, and lactic acids.
- Intestinal dysbiosis (candidiasis and SIBO-small intestine bacterial overgrowth) causes an intensive, constant, fermentation process through the release of lactic acid, toxic alcohols, and other acidic compounds.
- Diet-induced chronic metabolic acidosis caused by the consumption of processed foods, red meat, sugars, white flour and rice, and others.
- Chronic toxicity caused by acid-forming compounds, such as alcohol, some medications, environmental chemicals, and others.
- Dysfunction of the lungs, kidneys, skin, liver, and gastrointestinal organs, which are responsible for releasing acidic radicals.
- Dehydration and poor microcirculation.
- Chronic deficiency of the major electrolytes such as sodium, magnesium, potassium, and calcium.
- Low capacity of blood buffer systems and, specifically, the low capacity of bicarbonate buffer.

The CO2-bicarbonate buffer system (or the "bicarbonate buffer") is the main buffer system in the blood. It works as lung↕ **$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$** ↕kidney.

The pH of blood is steady, and human beings struggle to maintain a stable state to protect the vital organs, such as the brain, lungs, and heart, which completely stop if the pH in the blood drops even slightly. During metabolic acidosis, human beings make the intelligent choice to survive by saving the life important organs, such as the heart, lungs, and brain at the expense of peripheral "less essential" organs and tissues. The alkaline digestive glands pancreas and liver are affected most by changes in the blood pH because they manufacture pancreatic juice and bile, which are generally highly alkaline solutions.

Negative Effect of Metabolic Acidosis on Pancreatic Juice, Bile, and the Entire Digestive System

Under normal conditions, the pH of liver bile is 7.5 to 8.8, and the pancreatic juice has a pH of 7.1 to 8.2.[2] Consequently, the liver, gallbladder, and pancreas are the inner organs, directly involved in the body's acid-base balance. On the other hand, metabolic acidosis alters the bile and pancreatic pH in an unhealthy way, leading to serious digestion problems.

The Importance of Bicarbonate

To maintain the alkalinity of the pancreatic juice, the bile, the liver, and particularly the pancreas extract bicarbonates and minerals from the blood. The bicarbonate content is a key reason for the alkalinity of bile and pancreatic juice.

Content Of Bicarbonate (mEq/Liter) in Human Plasma, Pancreatic Juice, and Bile [3]

Body Fluid	Bicarbonate
Blood (plasma)	27
Pancreatic Juice	92–145
Bile	45

As seen in bile, and particularly in pancreatic juice, there is a lot of bicarbonate. The pancreatic bicarbonate output and duodenum pH are strongly interrelated. The interaction of digestive hormones, primarily secretin and cholecystokinin, with the autonomic nervous system regulates this very complicated mechanism.[4,7,8]

The researchers found that the pancreas and liver extract bicarbonate ions mostly from the blood. For instance, intravenously administered bicarbonate labeled with the C radioisotope appears rapidly in the pancreatic juice.[11] Experiments showed that "most if not all the bicarbonate of pancreatic juice must come from plasma." [4–6] There is substantial evidence that in pancreatic disorders there is a decreased amount of bicarbonate in the pancreatic juice and bile.[7, 9]

Duodenal acidity primarily depends on a lesser amount of bicarbonate in the pancreatic juice and bile. In chronic pancreatitis patients with exocrine pancreatic insufficiency, the duodenal pH is persistently low.[7,10] The pancreatic enzymes work only in the alkaline milieu.

The Optimal pH for the Activity of Pancreatic Digestive Enzymes [36]

Pancreatic Digestive Enzymes	Enzyme Optimal pH
Lipase	8.0
Trypsin	7.8–8.7
Amylase	6.7–7.0

Therefore, the acidic milieu in the duodenum where general digestion occurs is a central factor of indigestion. There is also a direct connection between the bicarbonate concentration and pancreatic juice flow and the elimination of enzymes.[11,12]

McClave believed that while healthy people have a high bicarbonate concentration in the duodenum, patients with chronic pancreatitis have low bicarbonate concentrations. In this case, the acidic fluid in the duodenum inactivates enzymes. Pancreatic lipase stops working if the duodenal pH is <4.5.[8]

Talamini adds a new possible risk factor for pancreatic cancer after chronic pancreatitis; namely, duodenal acidity. Patients with chronic pancreatitis frequently present with pancreatic exocrine insufficiency combined with a persistently low duodenal pH in the postprandial period. Duodenal acidity may raise the risk of pancreatic cancer in patients with chronic pancreatitis.[10]

The relationship between the rate of low pancreatic HCO_3^- secretion and high plasma H^+-ion concentration has been investigated in numerous experiments. A proportional relationship was found between HCO_3^- secretion and plasma pH. Different relationships were discovered between pancreatic HCO_3^- secretion and plasma HCO_3^- concentration during metabolic acidosis. Pancreatic HCO_3^- secretion fell to 41 $\pm$ 4% of that of the control during acidosis. The plasma H^+-ion concentration, therefore, seems to determine the rate of pancreatic HCO_3^- secretion. [35]

The importance of plasma bicarbonate is also illustrated by in vivo experiments in which pancreatic secretion was studied under conditions of metabolic acidosis. Canine pancreatic secretion was halved when the plasma bicarbonate was lowered to 16 mEq/L. [13]

Trypsinogen Activity and pH

Acidity also promotes the premature activation of trypsinogen (inactive enzyme) to trypsin (active enzyme) in the pancreatic ducts. Trypsinogen, like all other zymogens, is packaged in zymogen granules, which further retard trypsinogen activation. The high pH (an alkaline state) in the duct inhibits activation of trypsin.[14,15] The more alkaline the pancreatic juice, the higher the possibility of keeping trypsin inactive within the pancreas. Even a neutral pH of 7.0 can lead to this activation pathway. [16]

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Niederau and Grendellin suggested that the acidification of the pancreatic juice may play a role in the progression of acute pancreatitis.[17] Bhoomagoud et al. also suggested that metabolic acidosis may be a risk factor for developing pancreatitis. They confirmed experimentally in vivo and in vitro that decreasing pH (acidifying) increases the sensitivity of the acinar cells to zymogen activation.[18]

Both experimental and clinical observations suggest that acidosis may increase the risk of developing acute pancreatitis. Hegyi et al. further demonstrate that the failure of pancreatic ductal bicarbonate secretion (i.e., a decrease of the luminal pH) can increase the risk of or lead to pancreatitis.[37]

Magnesium is an alkalized mineral. Thus, it can attenuate the intracellular activation of proteases in the pancreas and lessen the severity of experimental pancreatitis when administered either intravenously or as a food supplement. A multicenter randomized controlled trial of magnesium sulfate in the prevention of post-ERCP pancreatitis shows the benefits of magnesium.[38]

Flushing Inactive Pancreatic Enzymes Stops Their Premature Activation

Another protective mechanism to prevent the premature activation of trypsinogen to trypsin inside the pancreatic duct is rapidly sweeping out zymogens from the pancreas. Washing out and draining pancreatic juice that is full of inactive enzymes and zymogens (trypsinogen) to the duodenum as quickly as possible is an essential mechanism to prevent premature activation of digestive enzymes inside the pancreas. This flushing mechanism is significant in protecting the pancreas from premature activation of the proteases and self-digestion and thus from the development of recurrent acute and chronic pancreatitis.

The duct cells lining the pancreatic duct secrete ions, fluid, and bicarbonate. A high concentration of ions causes water to enter the lumen by osmosis. Afterward, water flushes the contents of the pancreatic duct lumen (including zymogens) out of the pancreas and into the intestine. On the other hand, a low bicarbonate output can reduce the amount of water within the pancreatic ducts. This in turn raises the viscosity of the pancreatic juice and slows its elimination.

Matsuno et al. mentioned that bicarbonate plays a critical role in the viscosity of pancreatic juice. In patients with pancreatitis in which bicarbonate secretion and bicarbonate output declined, the viscosity of the pancreatic juice was considerably increased. They also believed that concentrated pancreatic juice can cause the progression of chronic pancreatitis.[7]

Acidification of Bile and Bile Refluxes

Bile secretion has similar regulatory and closed pathways for pancreatic juice. If the bile becomes extra acidic, it turns out to be very "aggressive." Precipitated bile acids in acidic bile corrode and irritate the bile and pancreatic ducts, the gallbladder, the ampulla of Vater, the sphincter of Oddi, and the duodenum.

Irritations of the duodenum's mucosa by precipitated bile acids lead to erosion, ulcers, and spasmodic, chaotic contractions, which dislocate the aggressive bile/pancreatic juice mixture. This causes spasms, bile reflux, refractory heartburn, irritation, inflammation, ulcers, and other symptoms. In a review of the refractory gastroesophageal reflux disease literature, Fass mentioned that experimental data support a role for persistent bile acids in the reflux as a potential factor involved in refractory heartburn.[40]

Aggressive, acidic bile/pancreatic juice mixtures often cause bile reflux, or backflow, into the pancreatic duct. Bile from the duodenum can flow upward, into the stomach and esophagus. Bile refluxes, which involve the duodenum, stomach, and esophagus, lead to inflammation, ulcers, and cancer.[19] Bile reflux often occurs along with stomach acid reflux, and together they are a horrible pair, inflaming the lining of the esophagus and potentially increasing the risk of esophageal cancer.[20,21]

Biliary pancreatic reflux occurs when the bile returns to the pancreatic duct. It activates proteolytic enzymes within the pancreas, and initiates acute pancreatitis and/or exacerbates chronic pancreatitis.

Rege and Moore found that the acidification of bile is a major factor in the development of gallbladder stones, which have been documented to block the bile and pancreatic ducts and severely damage the liver and pancreas.[22]

The Antimicrobial Activity of Pancreatic Juice Is pH Dependent

When the pH of pancreatic juice falls below 7.0, the antimicrobial activity is reduced. Rubinstein et al. found that the antibacterial activity of pancreatic juice was pH dependent.[23] Experiments on people with pancreatic fistulas showed that, under healthy conditions, pancreatic juice is practically sterile and destroys almost the entire spectrum of microorganisms.

There are remarkably few microorganisms in the small intestine because intestinal microbial homeostasis is controlled by a variety of factors. Pancreatic juice plays an essential role in limiting the number of microbes in the small intestine. There is evidence that the antibacterial action of pancreatic juice is extremely sensitive to pH, having an optimal activity at a pH of 8.5, which is an alkaline condition, and a complete cessation of activity at a pH of 7.0, which is neutral.[24]

Acidification of the pancreatic juice and decreasing pancreatic secretion makes the pancreas more vulnerable to infection. For that reason, the restoration of the alkalinity in the pancreatic glands is fundamental for the treatment and prevention of pancreatitis and further pancreatic cancer.[39]

Calcification

If chromic metabolic acidosis occurs, calcium is leached from the bones into the blood to neutralize acidity. The amount of calcium ions in the blood and body fluids increases, leading to the deposition of calcium in blood vessels and internal organs (calcinosis). This may explain the widespread simultaneous appearance of osteoporosis, arteriosclerosis, and calcification as calcium deposits in the inner organs. Calcification of the pancreatic gland is an important symptom of chronic pancreatitis.[34]

Precipitation of calcium salts within the pancreatic duct leads to stones, which irritate or block the pancreatic duct, causing inflammation or pancreatitis. Precipitation of calcium salts inside the gallbladder induces stone manufacturing and the obstruction of the sphincter of Oddi. This in turn can increase the pressure inside the pancreatic duct and activate proteases within the pancreas, causing self-digestion, damage, and pancreatitis.

Discussion: Clinical Implications

The authors believe that chronic metabolic acidosis kills the pancreas and the entire digestion process. Questions may arise from this hypothesis. Is chronic metabolic acidosis a widespread condition in the modern human?

Does chronic metabolic acidosis have clinical significance in everyday practice?

The authors believe that subclinical, low-grade, chronic metabolic acidosis is a widespread condition that is considered a "disease of civilization." Focusing on the acid-base equilibrium may be key in prevention and treatment of either digestive or hormonal pancreatic disorders.[1]

Metabolic acidosis is rampant in modern society. Mostly, this is due to the standard Western diet.[25,26] Most of what we eat now is acidic in nature and consequently changes the acid-base balance toward metabolic acidosis.[29] Nutrition scientists have described the incidence of metabolic acidosis in modern humans.[25,26,27]

For instance, researchers from the University of California found that most health problems stem from the deficiency of bicarbonate in today's food compared with the food of our ancestors.[26] Other authors have proved that current eating habits have produced low-grade metabolic acidosis in otherwise healthy people.[25–28]

Some authors found that metabolic acidosis increases with age.[30,31]

Currently, overacidity is frequent and can create harmful conditions that weaken all body systems. Chronic metabolic acidosis drives humans to ➤

leach alkaline minerals, including calcium, sodium, potassium, and magnesium, from inner organs, muscles, and bones to neutralize the acidity and to remove acid radicals from the body. The human being has only one way to recover from metabolic acidosis: to obtain extra minerals and bicarbonate to neutralize overacidity. Where can the organism obtain these minerals and bicarbonate? Naturally, people can only obtain minerals and bicarbonate from food, healing mineral water, and mineral supplements, such as magnesium/potassium.

If laypeople and medical practitioners understood that our alkaline diet requires mineral supplementation, healing mineral waters would be found in the US. Let us look at the experience of European medical doctors, who have treated a variety of digestive disorders with healing mineral waters for hundreds of years. The European public often spends their "healthful vacations" in mineral spas, where medical doctors evaluate the patient and prescribe the quantity, frequency, and temperature of healing mineral waters. In some European countries, insurance covers balneotherapy/mineral water cures.

The small town of Karlovy Vary in the Czech Republic has enjoyed hundreds of years of popularity as a famous healing mineral spa thanks to its thermal springs. In 1522, the first scientific medical book was published, and a regimen of drinking water from this spring was recommended for constipation. Since then, hundreds of clinical papers have been published describing the positive effects of this water on both animals and humans. Unfortunately, most of these papers are published in Czech, German, and Russian; thus, they are unknown by the American medical establishment.[32,33]

The demand for this water was so high that doctors in Karlovy Vary developed a vaporizing method to obtain genuine Karlovy Vary thermal spring salt 250 years ago. Dissolving this salt in the water makes it possible to use mineral water for healing at home. The water prepared from the genuine Karlovy Vary thermal spring salt has 40 essential minerals, trace elements, and bicarbonate in a proportion similar to that of human plasma. Czech doctors determined that the water manufactured from the genuine Karlovy Vary thermal spring salt had identical healing properties to the spring. European scientists and doctors have confirmed the positive effects of the Karlovy Vary healing mineral water on the pancreas and pancreatic digestive enzymes.[1]

Karlovy Vary healing mineral water is a natural alkalizing compound that helps the body to restore a normal pH by neutralizing acid radicals and removing them from the body. Before the insulin era, this water was the only healing remedy for diabetes. Karlovy Vary healing mineral water helped many Europeans with environmental and professional toxicity. Scientific research shows that this water decreases gas, bloating, stomach pain, abdominal spasms, and indigestion by increasing the production of bile and pancreatic enzymes and by opening the bile and pancreatic ducts, thereby decreasing internal toxicity.[32,33]

There are many complicated tests to identify overacidity in the body. More simply, one can observe positive pH changes in one's saliva and urine by using litmus paper at home. If the saliva and urine pH is less than 6.6 for one week, chronic metabolic acidosis and acidic pancreas and bile may be presumed.

Conclusion

Currently, the medical standpoint on digestive disorders narrowly focuses on the "hollow" organs, such as the stomach and colon, without paying attention to the "solid" digestive glands, such as the pancreas and liver. It is known from human physiology that, without a specific quality and amount of pancreatic juice and bile, the normal digestive process in the hollow chambers could not occur. The pancreas is the main organ of the entire digestive system. Almost all of the problems of the GI tract are closely related to the proper functioning of the pancreas. Therefore, a clinical diagnosis of gastrointestinal disorders de facto presumes pancreatic disorders.

Another very important consideration is chronic pancreatitis. Descriptions of the symptoms of this disease, including pain, steatorrhea, malabsorption syndrome, and weight loss, are found in almost all medical books, textbooks, and articles. The medical literature refers to this state as *pancreatic insufficiency*. It is known that these symptoms occur when only 10% of the exocrine pancreatic function is left intact. Unfortunately, this is not *pancreatic insufficiency*; it is *pancreatic failure*, for which therapeutic opportunities are very limited.

The final stage of chronic pancreatitis does not develop overnight. Typically, 8 to 15 years occur between the first attack of acute pancreatitis and pancreatic failure following chronic pancreatitis. Similar to disorders of other organs and systems, the initial disease stage of the pancreas does not present any structural changes. Nevertheless, after this stage, longstanding biochemical, biomechanical, neurohumoral, and inflammation responses lead to structural damage of the pancreas (chronic pancreatitis) and a lowering of the exocrine pancreatic function while bringing many accompanying digestive diseases. However, if 90% of the pancreatic functional capacity is reduced, pancreatic failure occurs with steatorrhea and malabsorption syndrome, resulting in a total crash of the digestive system and the entire human organism.

For the purpose of focusing on the early functional stages of pancreatic disorders, the authors propose the *functional clinical classification of exocrine pancreatic disorders*, which subdivides digestive disorders and diseases into three groups:

1. acidic pancreas and bile
2. pancreatic deficiency
3. pancreatic failure

On a daily basis in medical practice, crowds of people present with digestive symptoms that are consistent with those of patients in the "acidic pancreas and bile" stage of exocrine pancreatic disorders. Their tests are usually normal, and most of these patients receive palliative, symptomatic therapy. Restoration of the proper acid-base balance in digestive disorders may be one of the natural, pathophysiological approaches for functional dyspepsia, biliary dyskinesia, GERD, sphincter of Oddi dysfunction type III, IBS, and intestinal dysbiosis (candida overgrowth, SIBO), among others.

Pancreatic functional disorders are terra incognita in medicine; there is little attention on the functional stage of exocrine pancreatic deficiency regardless of the fact that the pancreas is a key organ in proper digestion. H. Worning wrote in *Digestion* that the prevalence of pancreatic diseases as the cause of dyspepsia varies in clinical practice between 0% and 25% to 30%. He believed that pancreatic function and pancreatic disease are closely related to various gastrointestinal diseases.[41]

The connection between functional gastrointestinal disorders such as functional dyspepsia, SIBO-small intestinal bacteria overgrowth, IBS, and impaired pancreatic function to a greater extent have attracted the attention of researchers and doctors for the last decade.[42–44]

Goepp et al. found low pancreatic elastase (a marker of exocrine pancreatic insufficiency) in 7.1% of the patients with irritable bowel syndrome.[45] Another point that low pancreatic function underlies dyspepsia and IBS is the beneficial effect of the pancreatic enzymes in these functional disorders.[46,47]

Smith et al. described abnormal Lundh tests in 27% of patients with functional dyspepsia. They wrote, "Pancreatic disease may explain the symptoms of some patients with non-ulcer dyspepsia."[48]

It is known that dyspepsia and functional dyspepsia are common conditions globally, affecting most populations, regardless of location.[49] Okada et al. considered that mild functional pancreatic disorders might trigger some cases with unexplainable chronic dyspepsia.[50]

Lindström et al. believe that, overall, 66% of the patients with abdominal pain had morphological and functional evidence of pancreatic involvement.[51]

Some researchers agree that differentiation between functional dyspepsia and early stage of the chronic pancreatitis is complicated.[52] Early-stage chronic pancreatitis and impaired exocrine pancreatic function are frequently misdiagnosed.

"Early chronic pancreatitis remains a diagnostic challenge as there is no gold standard for the diagnosis and pancreatic biopsy is risky and ➤

Acidity Kills

impractical. Reported data on the incidence and prevalence of chronic pancreatitis are unreliable and highly variable. Chronic pancreatitis is clearly under-diagnosed." [53]

The diagnosis of the early stage of the pancreatic diseases might be missed in clinical practice because symptoms of severe exocrine pancreatic deficiency are not specific at that time. There is no malabsorption syndrome or maldigestion, there is the absence of steatorrhea, and the pancreatic and liver enzymes levels in blood are normal. Therefore, early chronic pancreatitis is seldom suspected when pain is mild or absent, and there are unspecific symptoms of "dyspepsia."

Scientific research and clinical findings confirm that the pancreas and liver are more vulnerable to reduced functioning due to metabolic acidosis. One primary (ex juvantibus) therapy for multiple digestive and liver disorders is the mineral spa resort in Karlovy Vary and other resorts in Europe, and a great number of medical papers support the therapeutic action of the mineral/bicarbonate waters for digestive diseases. The pandemic of the digestive disorders in the modern world is associated with epidemic proportions of metabolic acidosis and dysbiosis, which form a vicious circle.

This article is an attempt to present the fresh, holistic approach that the pancreas is a vital organ for the whole body. We believe that our work may provide food for thought to many young researchers and health practitioners.

We cannot have optimal digestion if the body's system is acidic, because acidity kills the pancreas!

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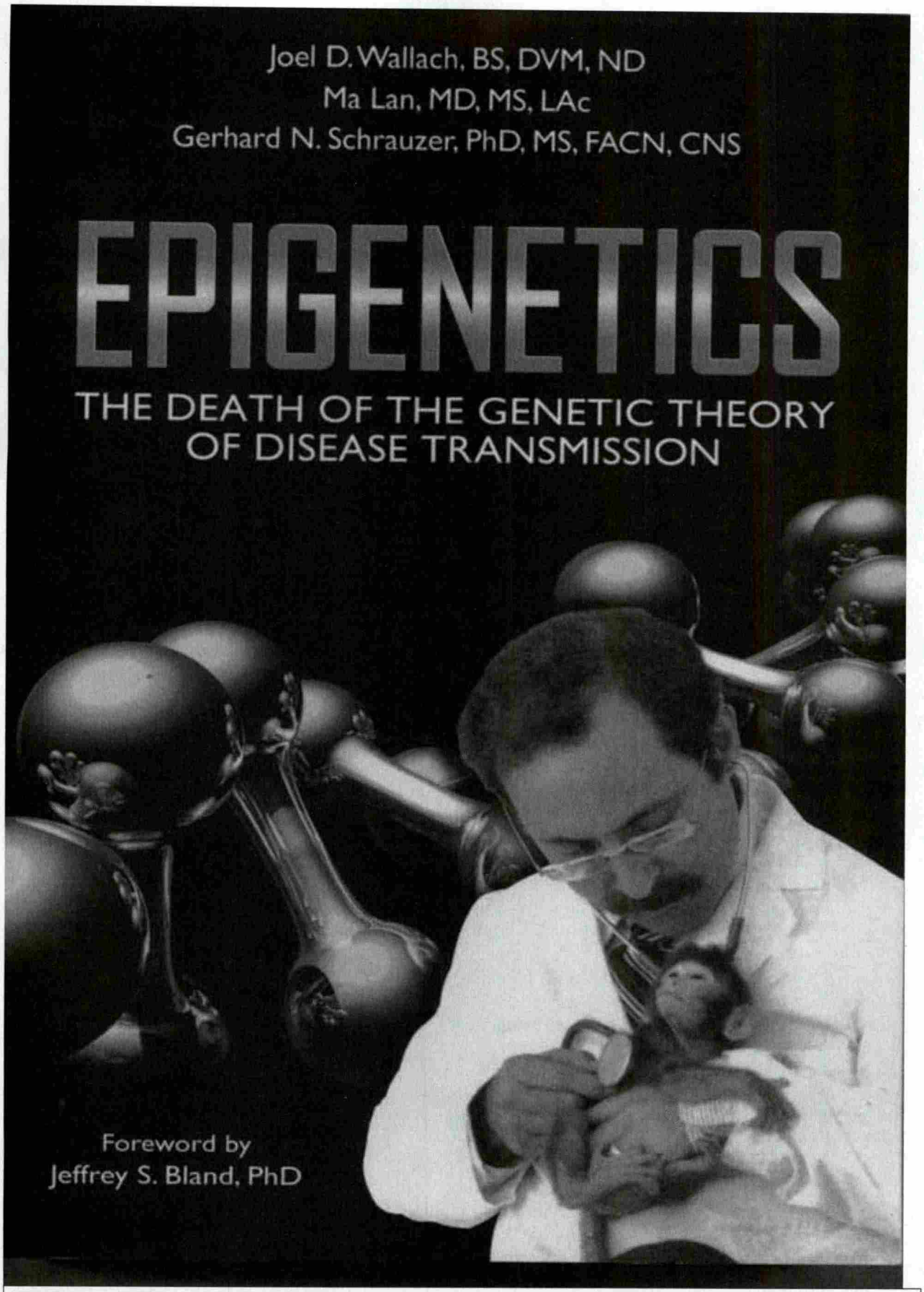
Peter Melamed, PhD, and Felix Melamed, MS, are licensed practitioners from Biotherapy Clinic of San Francisco. They are authors of the many articles on Internet, the book *Natural European Way of Whole Body Cleansing*, and the eBook *Healthy Pancreas, Healthy You* that consists of three interrelated parts:

I. *Structure, Function and Disorders of the Pancreas*
II. *Healing Food in the Digestive (Pancreatic) and Metabolic Disorders*
III. *How to Improve the Exocrine Pancreatic Function, Postpone Pancreatic Deterioration, and Heal Digestive (Pancreatic) Disorders*

In 1975, Peter Melamed established Biotherapy as a natural, holistic approach to healing. Biotherapy combines the wisdom of traditional Russian folk medicine, ancient Oriental medical therapies, and European naturopathy with cutting-edge Western technology. Biotherapy Clinic of San Francisco specializes in nondrug healing digestive (pancreatic), liver, gallbladder, and metabolic disorders.



Field Control Therapy: Successful Approach to Lyme Disease and Coinfections

Part 2

by Savely Yurkovsky, MD

Case 1

Mrs. B (see her quote in part 1, July 2015 issue) returned to an active lifestyle and work. However, the treatment course was neither easy nor quick, primarily due to the massive doses of antibiotics received previously in order to kill Lyme and coinfections, with both having successfully survived all of the "killings." In this regard, besides a wise admonition of the famed French physiologist, Claude Bernard ("The state of the body or terrain is everything, the microbe is nothing,") his fellow microbiologist and Nobel laureate in medicine Dr. Luc Montagnier with his colleagues have also alerted the infectious disease specialists to the following sobering facts:

> Pathogenic microorganisms in this day of age are not only submitted to high selective pressure by the immune defenses of their hosts but also have to survive under highly active antiviral or antibiotic treatments. Not surprisingly, they have evolved in finding many ways to escape these hostile conditions, such as mutations of resistance, hyper variability of surface antigens, proverbial biofilms, latency inside cells and tissues.[1]

Note that Professor Montagnier's research in homeopathy, based on conventional medicine, has yielded positive responses against microbes. Concerning treatment protocols to allegedly "better" overcome biofilms, cyst forms, and other bacterial defenses, scientific literature paradoxically states that the antibiotics themselves can lead to the development of bacterial biofilms! This is because antibiotics lead to candida infections that promote bacterial biofilms. Even though as an "insurance" antifungal drugs, herbs, probiotics, and other substances are added to antibiotics, there are dozens of *Candida* species, and to presume that an antifungal regimen is equally effective against all of these species equals to acting more in faith than in science.

Furthermore, not only do antibiotics lead to mutated bacterial infections that are far more difficult to treat, but *Candida* or other yeast species can mutate and turn into more aggressive forms too, following long-term antifungal treatments.

Considering the fact that human DNA evolutionarily originated from bacteria, viruses, and other microorganisms and the DNA of our mitochondria have still retained bacterial genes, antibiotic treatments represent a potentially large threat to both human immunity and health in general. Perhaps, that is why there is a direct, documented relationship between antibiotic use and cancer.

Scientific literature also states that antibiotics or any antimicrobial or meant "to kill" agents grant zero future host resistance against the infections being treated for. All these reasons are why I exclusively use homeopathic Lyme, *Babesia, Bartonella,* and other microbes, because besides being very effective in the short run and while restoring one's immunity, homeopathic antimicrobial stimulation can also lead to much better future immune resistance. This has been confirmed by scientific studies, with one involving even as many as 2.3 million people to prevent a deadly infectious disease wherein an effective long-term antimicrobial resistance was successfully achieved.[2,3]

The latter proved even more effective than a conventional vaccine while being 10 times cheaper, but conventional medical journals refused to publish this study without offering any reasons for rejection. However, in chronic diseases such as Lyme, use of homeopathic vaccines alone can fail or even backfire if one ignores the state of existing immunosuppression. Many other non-Lyme infections, as was the case with this and other patients, were identified and treated because these greatly add to and sustain the state of immune deficiency, due to several main mechanisms:

1. They overburden the immune defenses.
2. They, in addition to Lyme, release mediators that impair different immune defenses.

3. They enhance the state of general inflammation that often leads to the increase of electromagnetic sensitivity, which both by and of itself and in conjunction with mercury and other toxic metals exert significant immunosuppressive effects.

Case 2

Woman in her 60s presented in a state of formal Morgellons disease with colorful fibers coming out of her face and scalp, plus a slew of debilitating symptoms: fatigue, pains, depression, hypertension, and others, for years. All prior treatments for Morgellons had failed and Lyme diagnosis was missed. A good quality of life has been returned to her following the series of treatments, along with significant progress in her overall health, with Lyme disease not being an issue anymore.

Case 3

Man in his 40s diagnosed with Lyme shortly prior, yet stating that he likely had it since he was in his 20s. He experienced poor memory, anxiety, neurological symptoms, decreased vision, poor energy and sex drive, and head and back pains. Tried many natural treatments without success. After a fairly short series of FCT treatments, he reported feeling the best he had in years and practically symptom free.

Case 4

An alternative practitioner in her 40s with a state of head to toe problems for several years: decreased memory, burning mouth, fears, knee and back pain, headaches, hypoglycemia with sugar cravings, thyroid problems, poor energy, and inability to lose excessive weight. After only a few treatments, she reported feeling "the best ever in my life."

Case 5

Woman in her 40s with massive body breakdown, over the years, and a diagnosis of possible Lyme. Her state: periodic fevers, debilitating back pains, fatigue, headaches, phobia, anxiety, abnormal space perception, food allergies and cravings, multiple infections – parasitic, bacterial, viral – enlarged lymph nodes, and a neurological voice disorder. Many prior treatments were of no help. Yet, in spite of her inconsistent dietary efforts and poor genetics, after some dozen FCT treatments, she reported: "I feel so much better than when I started with you. I keep being amazed by it."

Case 6

Woman in her 60s with generalized joint pains, chronic anemia and fatigue, treated by her rheumatologist with two anti-inflammatory drugs for rheumatoid arthritis, for years. Diagnosed through bioresonance testing as having Lyme, among other causes. Within a year, she came off both drugs, has had her anemia resolved, and quality of life progressed to normal.

Case 7

Man in his 50s frequented emergency rooms with typical heart angina pains. All heart tests, including coronary artery catheterization performed at a prestigious university heart center, turned normal and his cardiologists were puzzled. Following brief FCT treatment for Lyme, based on bioresonance testing findings, his chest pains ceased.

Case 8

Middle-aged woman suffered from debilitating migraine headaches for many years. The big part of this was missed Lyme infection in the brain. The outcome: no more migraines.

Case 9

Woman in her 60s, a very intelligent former UN executive, in a state of complete personality change with severe depression, anxiety, panic attacks with crying, obtrusion of cognitive function, blurred vision, sensation of inflamed brain, arthritic pains, fatigue, dizziness, inability to read due to poor focus and not retaining information afterwards. After 2 years of unproductive rounds through conventional specialists, she was finally diagnosed with Lyme and coinfections by an integrative MD. Weeks of several antibiotic treatments along with supplements resulted only in a mild improvement of depression and anxiety.

I advised that she stop all antibiotics, due to the detected side effects by bioresonance testing, and supplements. However, even though she wanted to finish the course of antibiotics out of fear, she had to discontinue one of these anyway, admitting that she did feel its side effects. Following her first FCT treatment, she reported that her arthritis, panic attacks with crying, and inflamed brain were gone, and she experienced an increase in energy and focus, with brain fog and dizziness becoming almost a nonissue. She also stated: "I can tell you that on your drops, especially the Lyme ones, I felt much more Herxheimer reaction than on my antibiotics." Following discontinuation of her second antibiotic and receipt of another FCT treatment, she reported that her problems were gone.

Case 10

A young woman who reported her invalidlike state reflected in Ms. C's quote in part 1 of this article (July 2015). After her visit, she very reluctantly followed my advice to stop all of her antibiotics for Lyme and coinfections. Following only her first treatment, with two successful and in total so far, she reported having ceased looking and feeling like a corpse, and even experienced the return of her sex drive, which she had lost 5 years prior, from the onset of Lyme. She also reported much improvement in her pains and decreasing her narcotic painkiller, and in her internal body vibrations and muscle twitches which she had suffered after using an electrocuting machine for Lyme. She too noted stronger Herxheimer reaction to homeopathic drops, compared with all of her prior antibiotic regimens.

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Lyme Disease and Coinfections

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Case 11

Man in his early 60s with multiple medical problems: sinusitis since infancy, fatigue in the afternoon for decades, brain fog, arthritic pains, and chocolate cravings, all for years. All these were resolved in 8 or 9 visits.

Case 12

15-year-old boy treated with several courses of antibiotics for Lyme disease. However, all of the complaints persisted: fatigue, headaches, arthritic pains, shortness of breath even when only walking, low appetite, difficulty keeping up with schoolwork. All of these were resolved after 2 or 3 treatments.

Case 13

Man in his late 20s, athletic trainer, complaining of fatigue, depression, panic attacks, left sided body heaviness and brain fog, all for many years, a decrease in short term memory, motor speech problem and brain-body detachment for years. He has received more than half a dozen psychotropic drugs over the years and was still on a few. After 8 months of the treatment, reported being off psychotropic drugs, for 4 months by now, for the first time in the last 12 years. Most of the problems are gone, others are better or much better, but by his admission: "My workplace is so loaded with computers and fluorescent lights which drain me and I feel it slows my complete recovery."

Case 14

A woman in her 30s, with debilitating symptoms for years, diagnosed with Lyme disease and *Bartonella* some 2 years prior to this visit. She was unsuccessfully treated with bouts of multiple and prolonged antibiotic treatments, as well as alternative approaches by her integrative MD. Her condition involved massive pains, severe neurological symptoms and fatigue, gaining much weight, food intolerance, respiratory and vaginal infections, severe mental impairment and brain fog, falling down after taking even a few steps, experiencing auditory hallucinations of birds chirping, loose bowel movements, and depression. Her integrative MD was planning on placing her on a special Alzheimer's alternative and conventional (pharmaceutical drug) program.

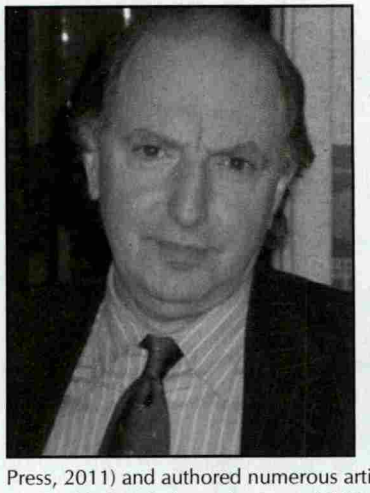
But, besides Lyme, my bioresonance testing, as always, detected a slew of other unhealthful items especially affecting her brain: pesticides, herbicides (she lived in farm country), solvents, mercury, and one of the flu viruses. Following a single treatment, she reported that she stopped falling down, she had a substantial increase in energy, her auditory hallucinations of chirping birds disappeared, her bowel movements normalized, and she experienced a disappearance of the obtunded Alzheimer's-like mental state with an increase in mental clarity and word recall, as well as overall feeling much healthier and happier.

Case 15

A middle-aged woman in a state of chronic facial pains and twitches, fatigue, anxiety, fears, headaches. She was treated by an osteopathic doctor, a book author and specialist in chronic pain disorders, without success. Among other causes, bioresonance testing identified Lyme affecting her trigeminal nerve in the face and TMJ. She responded to the treatment very well and has attained normal life as well as her osteopathic doctor's unselfish support for FCT.

Case 16

A 9-year-old girl was referred to a psychiatrist for psychotropic medications by a surrendered child psychologist because of the girl's restlessness, OCD, aggression, moodiness, and overall unpredictable behavior, which all continued getting



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.

worse over the years. Bioresonance testing found Lyme infection present in the brain, among other causes. She was 90% cured after a single treatment and completely after the second one. "She is just normal. Huge change, huge, huge, since we came here," said the mother.

Summary

From these reported and many other tested and treated patients over the years, it seems evident that Lyme disease and coinfections represent only a segment, however significant, but not even nearly a total disease. That is why the success of these reported cases was predicated on identifying and properly addressing other important segments of this total disease. These, among others, include toxicological agents and other infections, electromagnetic stress, and many dysfunctional exhausted organs. That is why, in these cases anti-Lyme therapeutics were not used alone, but only in conjunction with other important measures to address the totality of the *individual* sick state of the body.

Concluding where we started, lessons from the philosophy of science, it is to state that it is not bioresonance testing, per se, that makes the difference in important diagnostic findings, as too many alternative practitioners still seek or even claim that they have found the best one, as if there was some Kentucky Derby winner in this field. But the truth is such "best" bioresonance technique, machine, or method, including FCT's, does not even exist. It is a *theory* behind the test, like quality of questions asked through a microphone and not the microphone itself, which matters. The same with treatments, it is not just "homeopathics" or "homeopathy" or "special remedies," all of which can be used in hundreds of different ways, but a sound theory that dictates which ones are the most effective based not on "homeopathics" at hand, but on the primary needs of individual patients' disease states.

So, keeping all of these important elements in mind and even while Lyme disease with coinfections do represent a notorious, powerful multiheaded hydra with its uncanny ability to regrow its heads, following medical attacks, it can be successfully defeated through a more encompassing and different medical approach, as the experience presented here has deemed.

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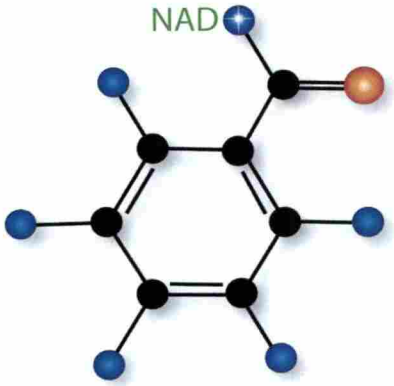

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Salicinium: A Powerful Biological Response Modifier in Cancer

by Carol M. Brown, DO, PhD, FAARFM

My introduction to Salicinium was an abrupt episode, but the beginning of a dramatic change in my practice. A few years earlier I had provided high-dose vitamin C to one of my patients with a 6-year history of ovarian cancer. She had been treated at the Issels Clinic in California, and the cancer had been stable for over 2 years. She and her husband had also experimented with various other alternative treatments since her diagnosis and the discovery of her intolerance to the routine conventional regimen. It was about a 90-minute drive from their home in Chicago to our clinic in Milwaukee, so she came for IVs rather sporadically. Two years later, as her cancer was progressing, I received a call from her husband stating that there would be a new IV regimen coming by FedEx to my office in the morning, and asking if I would give it to her. I scrambled for information; and, after studying the data and determining that it was safe, I administered it to her a few days later. She felt better and was ambulatory by the end of the 3-week IV regimen but again her treatment schedule was inconsistent and she was lost to follow-up after about 6 months.

At that time, my practice consisted primarily of patients with difficult conditions who were not adequately improving or worsening and who sought "another way." I did not specialize in treating people with cancer, though I had taken a fellowship in integrative cancer therapies to learn to support those trying to overcome cancer without medical intervention. I was intrigued with the patient's response and the ease of administration of the Salicinium. She had no adverse effect except for the day that her immune system "woke up" and she had 2 to 3 hours of chills and achiness. It seemed so clean – using a natural product with the potential to stop cancer. During the next few months I researched cancer and Salicinium as a way to help my other patients.

As physicians, we always seem to be looking for ways to "kill" something, but forget that we are already endowed with the greatest killing mechanism ever created – our own immune system. In fact, we have spent the last hundred years trying to determine how to help (or cause) our killer cells to attack invaders for which the immune system appears not to be programmed. Some of the latest studies are directed entirely toward programming an individual's immune globulins to recognize their own particular cancer.

Could the immune system *already* be programmed to handle this problem? Are there other diseases or pathologies that we can look to and find answers to this dilemma? Is cancer really the problem or is it a victim, just as we are when it resides within us? Can we look to the past to find answers which will change the future?

As a PhD I was taught to study a subject, take it apart, and study it again and again. While beginning my studies on cancer I ran across the term *trophoblastic thesis of cancer*. In looking up literature on the subject I found a document titled "An Inquiry into the Trophoblastic Nature of Cancer," by Peter W. Stacpoole, 1971. While reading this document, I was stunned to find the forerunner of one of today's answers to the nature of cancer. On pages 15–16 I quote in full:

> The distinct invasiveness of the trophoblast and the intimacy of the junctional zone are associated with a characteristic fibrinoid material, probably of trophoblastic origin (Kirby et al. 1964; Bradbury et al. 1965; Currie and Bagshawe 1967; Curie et al. 1968; Bradbury et al. 1969) which exists as a sort of acellular barrier between maternal and trophoblastic tissue and which may act to limit the invasiveness of the trophoblast (Wynn 1964, 1965, 1967). *The fibrinoid may be mucopolysaccharide in nature, since normal pregnancy trophoblast (as well as "malignant" trophoblast) is known to exhibit a pericellular coat,* rich in sialic acid (Currie and Bagshawe 1967; Currie et al. 1968; Billington et al. 1969; Bradbury et al. 1969). It is thought that this *sialomucin coat* protects the genetically foreign trophoblast and fetus against maternal *lymphocytic attack* by electrostatic repulsion of the lymphocytes,

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by physically masking the trophoblast's antigens or by some other mechanism (Simmons and Russell 1962; Currie and Bagshawe 1967). (emphasis mine)

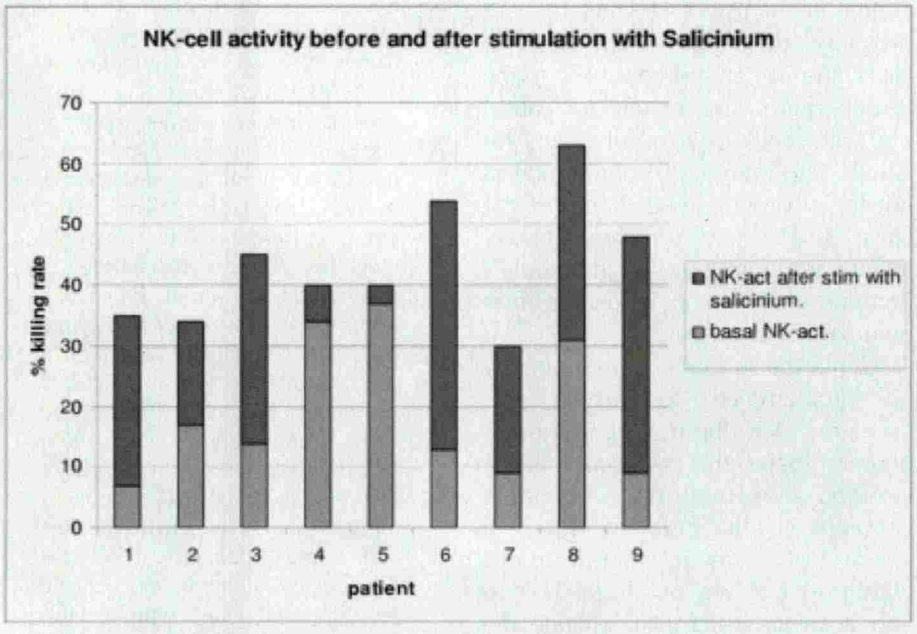
It doesn't take an inquiring mind long to realize that this "fibrinoid material" is the beginning of the search which has led us to alpha-N-acetylgalactosaminidase, or nagalase for short. This enzyme is not only the primary protective agent for cancer cells but also the single item that allows life as we know it to keep going on this earth. It is the protection for the trophoblast (cytotrophoblast) of the placenta. It is also the very enzyme that our muscle cells *instantly* excrete upon the inability of the mitochondria to manufacture ATP due to a lack of respiration. Without this function, our muscle cells would be recognized as diseased or foreign cells and be phagocytized by our own immune reactions. There would be no mammalian life if it were not for nagalase.

Since the beginning of inquiry into the nature of cancer, another unexpected factor has baffled the best of scientists: why, when returning respirating cells – which had been made to ferment in vitro by lowering oxygen pressure by 35% (anaerobiasis) – back to a normal oxygen pressure, did they return to respiration and not remain in fermentation? This type of cell is referred to as a *facultative aerobe*, a cell able to live with or without oxygen, because it can metabolize energy either way. It prefers aerobiasis over anaerobiasis, but can continue to live for a period of time until oxygen can be restored, thus respiration. This is why our muscles remain sore for a period of time after being overused. The production of lactate accumulates lactic acid in the tissue until oxygen is returned and normal cellular respiration is resumed.

The problem here is this: if oxygen is not returned in time (and no study has been done to find out how long that may be), the mitochondria are harmed and cannot return to full respiratory function, so the facultative cell remains at some level of fermentation. The facultative anaerobic cell can still produce nagalase for protection from the immune system. It still maintains the function of division, but it cannot reproduce something for which it no longer has functioning chromosomes. This cell can now only reproduce cytoplasmic functioning cells. The further these cytoplasmic cells divide, the more purely anaerobic they become. It has always been said that these cells become *obligate anaerobes*, a cell that can be poisoned by oxygen. This terminology is incorrect. These cells become *aerotolerant* cells, as they make energy without oxygen, and unlike obligate anaerobes, they are *not* poisoned by oxygen. Because of this single difference, they can go anywhere that they are carried and not be bothered by the immune system or even greatly raised (hyperbaric chamber and other) oxygen levels (Hogg S. *Essential Microbiology*. 1st ed. Wiley; 2005:99–100.)

On this note, if one disbelieves this factor, one must ask oneself, how can cancer stem cells and cancer tumor cells metastasize all through any part of mammalian tissue, away from the acidic milieu of the cancerous process, and survive in a much higher oxygen atmosphere? It is because these cells are manufacturing their own microcosmic atmosphere (nagalase) and are *aerotolerant*. These two factors (the returning of cells to normalcy and aerotolerance) have misled science for all these years as humankind has tried to understand and devise control over the cancer scourge.

Consider the following: the nagalase coating (which is actually alpha-N-acetylgalactosaminidase) is an enzyme containing the glycome N-galactosaminidase. When a phagocyte carrying N-galactosamine comes close to a fermenting cell, it is repelled as *like repels like* because the phagocyte also carries N-galactosaminidase (Currie and Bagshawe 1967). Phagocyte repelling has been known for years, but what wasn't known is the composition of the vitamin D3-binding protein containing three sugars: one galactose, another sialic acid, and N-acetylgalactosamine, which is deglycosylated by nagalase, effectively stopping the production of GcMAF from vitamin D. Thus, as the old phagocytes die, new ones are



*Patients 4 & 5 were control patients with no cancer.

prevented and immune suppression begins. This happens very slowly at first, but becomes rapid as the process gains ascendancy. When studying GcMAF, I was interested to discover that *other entities also producing nagalase for their protection*; for example, HIV, HSV-1/2, influenza, hepatitis C, and oddly enough, if certain cells are infected by a virus, cells themselves. This demonstrates that cancer and fermenting cells do not have exclusivity.[1]

So once again we ask ourselves the question, is the immune system *already* programmed to handle this problem? The answer is of course, *no*. If it were, there could be no life as we know it. It also means if, in the natural course of things, the immune system were not supposed to have an effect on these things, then something very unnatural such as cancer cells has happened. In other words, we should not look to the immune system for fault, but elsewhere. What can we find in nature to change the course so that phagocytes can operate as they were intended?

It is not the purpose of this article to dwell on prevention – which of course has proved to have failed miserably – but to identify a way of allowing the immune system to do what it was intended to do best: keep the mammalian body functioning disease free. The cells that fail to return to respiration gradually become victims to permanent fermentation and eventuate into the process which ultimately victimizes us: cancer.

The truth is that the immune system *is* working as intended. However, we are still compelled to find something to interfere with the debranching enzyme nagalase. If nagalase can be disrupted, then the phagocytes of the immune system would be able to proceed with *lysing* of the fermenting cell. At the same time, more phagocytes would be signaled to the area and begin deconstructing the now vulnerable naked cells.

Upon entering the world of Salicinium, I wanted to understand its effects. I learned from certain scientific publications that a fermenting cell, due to the greatly increased requirement for an almost all-glycome diet, will transfer some of its large GLUT-4 insulin receptors from the inside lining of the cell to the outside lining to allow vastly increased amounts of sugar to enter. The external location and the larger size of the GLUT-4 transporters allow larger, complexed molecules of sugars to enter the needy fermenting cell. These complexed molecules pass the debranching enzyme as they are delivered through the inside lining of the cell and sugars are separated from their associated complexes. Are you beginning to see the requirement for a lot of sugar in the cancer/immune process? Once passing the debranching enzyme, the glycome is picked up by hexokinase and phosphorylated by ATP to become glucose-6-phosphate.[2,3]

The First Immune System Biological Modification by Salicinium

Salicinium is a glycobenzaldehyde.

In the food chain, there are many things that contain *aldehydes*. Aldehydes are protective to many foods, and nature has allowed our metabolic system ways to detoxify them, mostly through the liver. However, *benzaldehydes* are different and very toxic. Benzaldehyde *never* gets inside normal cells and is slowly detoxifiable by the liver. Complexed with glucose, it is harmless to healthy aerobic cells. However – in the case of a fermenting cell – a benzaldehyde glycome will be drawn in through the GLUT-4 receptor and be intercepted by the debranching enzyme to separate the glycome for use and the benzaldehyde is set free. It must be detoxified. Remember this is not aldehyde. It is benzaldehyde!

Glucose-6-phosphate is active in the cytosol pathway as it is in any cell, normal or fermenting. But in a fermenting cell, the out-of-the-ordinary benzaldehyde is attracted to the next step of the energy pathway: NADP+. NADP+ is the detoxifier for aldehyde as well as an intermediate step to 6-phosphoglucono-lactone. Normally NADP+ picks up a hydrogen atom from glucose-6-phosphate and becomes NADPH. However, when it attaches to a hydrogen from benzaldehyde it becomes NADP-benzaldehyde, *an intolerable situation*.[4,5]

This can best be best explained by quoting from Salway's book *Metabolism at a Glance*, Chapter 12, page 32: The pentose phosphate pathway:

> The pathway can be considered in two phases: the *irreversible oxidative phase* comprising the reactions catalyzed by glucose 6-phosphate dehydrogenase, lactonase and 6-phosphogluconate dehydrogenase; and the *reversible, non-oxidative phase* involving the rest of the pathway, then: Regulation of the pentose phosphate pathway: The flow of metabolites through the pathway is regulated at the glucose 6-phosphate dehydrogenase reaction and the 6-phosphogluconate dehydrogenase by the availability of NADP+. Therefore, in red blood cells for example, the flow is linked to the ability of NADP+ provided by glutathione reductase; the latter is needed to produce reduced glutathione, which protects cells from oxidative damage. In liver it is regulated by the availability of NADP+ supplied by fatty acid synthesis." (emphasis mine)

This same principle is identical for *any* fermenting cell.

This is an irreversible act in the metabolic pathway. The process of making four ATP from one glucose and two ATP has now faltered. When this happens, the fermenting cell is not dead, but it is beginning to starve for energy. While in this precarious position, the amino acid protein necessary for the production of nagalase cannot be produced and the protective nagalase coating is lost. Now exposed and ready for recognition, the cancerous cell is doomed. ➤

Salicinium

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The Second Immune System Biological Response Modification by Salicinium

Salicinium was tested by the German laboratory BioFocus and compared with the best-known immune-stimulating product – Lektinol. Salicinium increased the NK cell activity attained by Lektinol by nearly double in all cases. Also included were test samples from two persons without cancer, and these two controls also increased the activity of NK cell activity. One would expect an increase in the *number* of natural-killer cells if nagalase levels were lowered as well, but that would be a much slower process.

This proves the second biological response modification attained with Salicinium.

On March 25 of this year, I presented at The Best Answer for Cancer Conference in Reno, Nevada. While there I had the privilege of meeting several other physicians who also use Salicinium and shared findings. I was also able to meet with Ioannis Papasotiriou MD, PhD, head of the molecular biology department of Research Genetic Cancer Centre (RGCC). Its lab has tested Salicinium on blood from more than 5000 cancer patients, and Salicinium has maintained an incredible kill rate against cancer stem cells (CSCs) and circulating tumor cells (CTCs), with more than 80% of patient samples' being sensitive and no form of cancer not being affected. A single dose provides a 48-hour kill rate of about 26%. That's one dose!

Papasotiriou believes that there is more to be learned about Salicinium and is excited about the reproducibility and response to it.

My experience has been very good as well. I have nearly a 70% survival rate. I will share a few patient experiences:

Ken, 48-Year-Old Male

2010: Adenomcarcinoma of protocaval region/unknown origin. Initial treatment at Mayo for possible pancreatic cancer with surgical resection and chemotherapy.

January 2014: Presented to our clinic with recurrence. Afraid to be retreated conventionally due to lack of specific diagnosis and concern for further inadequate treatment. Wife looking for alternatives. General health OK. IV Salicinium protocol completed 3 weeks later. He is well, back at work since February 2014, hunting, enjoying life with his wife, and following recommendations carefully. Initial nagalase test result was 2.00. Present nagalase test result is 0.87.

Slobodan, 67-Year-Old Male

2013: Cirrhosis/stage 4 liver cancer w/mets to chest wall and spine. Tx Nexavar palliative care advised – unable to tolerate Nexavar. "Inoperable." Wife – breast cancer survivor – treated in Mexico 12 years ago, now alive and well. Sought nontoxic treatment for husband but currently unable to afford foreign (US) health care.

Began Salicinium December 2013. Completed protocol August 2014. PET scans normal in June 2014. Bone scan unremarkable June 2014. Initial nagalase – 1.40. Present nagalase – 0.67. Alive, active, and well.

Jamilla, 48-Year-Old Female

2012: Stage IIB moderately differentiated invasive ductal carcinoma ER/PR 100% positive HER-2/neu negative left breast cancer. Husband naturopath – treating alternatively – unable to resolve – condition progressing. Surgical resection in New York (to avoid pretreatment with chemotherapy). Positive sentinel node.

Began Salicinium July 2013. Completed protocol September 2014. Thermograms negative. Mammograms negative. Initial nagalase – 2.60. Present nagalase – 0.72. Alive, well, full-time work at Southwest Airlines. Husband happy.

Note: If you don't quite grasp how Salicinium works or are somewhat a visual person (as I am) and would like to see precisely what happens *after* Salicinium has modified the immune reaction, unblocking the immune reaction, please go to http://www.youtube.com and type "ntk8XsVIDe0" exactly as shown here (last character is a zero) in the search bar.

This recent video created by the University of Cambridge (UK) shows exactly what happens first to the cancer stem cells, then to the circulating tumor cells, and finally the primary cancer (in that order) when they are attacked by a body's cytotoxic T cells.

Notes

1. Yamamoto N, Urade M. Pathogenic significance of alpha-N-acetylgalactosamine activity found in the hemagglutinin of influenza virus. *Microbes Infect.* 2005;7:674–681; Yamamoto N. Pathogenic significance of alpha-N-acetylgalactosamine activity found in the envelope glycoprotein gp160 of human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses,* 2006;22:262–271.
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Dr. Brown began family practice in 1985 in Milwaukee, Wisconsin, with one of her ER colleagues. She began practice in 1989. During this time she continued to practice full-time emergency medicine and subsequently obtained board certification in emergency medicine. In 2003 she experienced an epiphany that changed her life and the course of her practice to integrative medicine where, she believes, healing is truly possible. She has since poured her life into the study of science-based alternative medicine. She obtained a second doctorate in 2005 and a second board certification in anti-aging and regenerative medicine in 2008. She has developed an exceptional and comprehensive practice, CMB Health Specialties.Dr. Brown is currently enrolled in a fellowship in Brain Health and recently completed a fellowship in integrative cancer therapies. Dr. Brown maintains clinical professorships at Marquette University, UW Milwaukee, and Midwestern University in Downers Grove, Illinois.

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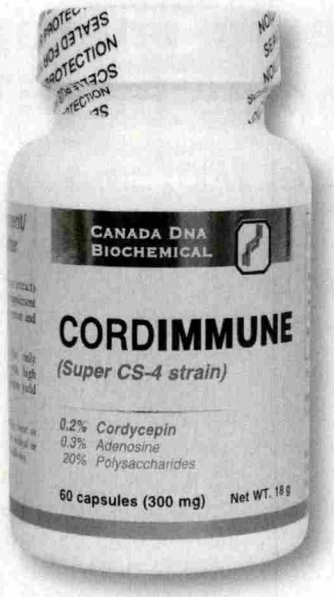

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Angiogenesis: Cause or Effect?

Companion Diagnostics and Surrogate Markers for a Novel Antiangiogenic Therapy Multitargeted Epigenetic Therapies (MTET)

by M. A. Nezami, MD; Daniel E. Stobbe, MD; and Aron Gould-Simon, MD

Patients with cancer are evaluated through different oncology laboratory markers, aiming at translation to clinical findings, to evaluate progression of disease as well as translating to overall survival, as surrogate markers. This effort has been revolutionized as the traditional measurements of the tumor size in CT scans, and identifying cancer response by Response Evaluation Criteria in Solid Tumors (RECIST), has failed to effectively translate into patient survival. Therefore establishing the prognosis in majority of patients, especially with heterogeneous tumors, has been extremely challenging.

One area of most recent attention in identifying surrogate markers has been the vasculogenesis and its related serum markers. Different stages of carcinogenesis and metastasis is greatly dependent on tumor angiogenesis, as a result of vascular endothelial dysfunction. Novel ways to assess vascular function in cancer include measuring levels of circulating endothelial cells (CEC) or circulatory tumor cells (CTCs). The presence of CEC has recently been recognized as a useful marker of vascular damage. CTCs can induce endothelial colonies and may contribute toward vasculogenesis. Increased vasculogenesis increases CTC viability, in a vicious cycle. Also, as the circulatory tumor cells transition to mesenchymal cells, their tendency towards vasculogenesis increases. Such transition appears to be dynamic and under the influence of stroma.

Secondly, there have been efforts to correlate FDG-PET scan findings with patients' prognosis. That said, unfortunately there is no direct translation to survival, especially in heterogeneous tumors.

The current understanding of the previously described Warburg effect suggests increased *hypoxia* as a driver for tumor growth, as a common signature of highly malignant tumors with capacity to metabolize glucose quickly, to lactic acid. This pattern can be related to increased glycolytic enzymes activity. One recent finding was that activated hypoxia response elements (HRE) by hypoxia can activate hexokinases. This phenomenon could potentially translate into increased SUV findings at FDG-PET scan.

Our understanding of heterogeneity of tumors has led us to look more in depth at cancer stem cells and epidermomesenchymal transition (EMT). Logically, the tumors which have higher heterogeneity have higher stem cell potentials and increased EMT transition. Here again, hypoxia and related hypoxia-induced factor (HIF-1) can also be the promoter or origin of such increased activity in downstream targets, through Wnt, Snail, and Slug pathways increasing the tendency of tumors to show more heterogeneity.

That said, as of today, there is not a single biomarker used clinically for assessing vasculogenesis, or intratumoral hypoxia and the correlation between FDG-PET findings and survival has not been strong, especially in more heterogeneous cancers (such as breast and lung cancer). Several studies have failed to show direct harmony in CTC findings and FDG-PET (although in breast cancer some studies have shown some but not strong relationship between progression of disease in PET and increased CTC, when CTC has been less than 5). The same is true for NSCLC. In NSCLC (due to heterogenic features), we see discordant relationships, between CTC and FDG-PET findings, described in the literature as the more aggressive cases, can have less CTC readings, and vice versa, and there is very poor correlation of CTC with PET findings.

Here we hypothesize that serum/plasma vascular endothelial growth factor (VEGF) measurements, as a biomarker for vasculogenesis (and possible intratumoral hypoxia), before and after therapy independently, or in addition to, circulatory tumor cells assay, can be used as a prognostic marker correlating with FDG-PET findings. This could become a meaningful companion diagnostic tool to translate to clinical outcome, and overall survival.

This is also important in therapeutic areas, as traditional chemotherapies in general (all anthracyclines, alkylators, platinum-based chemotherapies, etc.) increase the serum circulatory tumor cells, as well as serum VEGF, by several mechanisms, including pro-inflammatory cytokines, disrupting the

tumor vessels by disrupting endothelial dysfunction and causing tumor cell leaks. This necessitates new tools to overcome such negative measurable impact on potential survival.

Accordingly, here, we present a summary of 100 cases of advanced disease, and we present in detail three cases of patients with heterogeneous stage IV breast cancer who had failed several lines of chemotherapy and were treated using a novel antiangiogenic therapy consisting of natural and off-label drugs. These are known to inhibit hypoxia-induced pathways, in a protocol called multitargeted epigenetic therapy (MTET), resulting in independent and synergistic response identified by serum VEGF/CTC/ and FDG-PET combo findings, and translated to improved progression-free or overall survival.

We conclude that this sample presents considerable effect size and can affect the current practice of oncology by providing better prognostic and therapeutic tools targeting angiogenesis in refractory heterogeneous disease.

- As of November 2014, 100 patient charts were selected and reviewed retrospectively. The inclusion criteria were diagnosis of cancer, and receiving minimum of 2 weeks of treatments per protocol. No patients were excluded. Patients were aged 18 to 83 years. All were diagnosed by their oncologist/physician and were offered standard conventional treatment of surgery, traditional chemotherapy, or radiation. Out of 100 patients, for 62 patients (62%) there were no actual treatment options available for them (except palliative care) due to severity of the disease and failure to respond to the standard of care, including chemotherapy.
- These people had stage IV disease with multiple micro- or macrometastatic disease or had relapsed after unsuccessful therapies. Progression or recurrence of disease was manifested by their tumor markers and scans.

The following results were obtained during or after completing the course of therapy:

Imaging response (PET), decreased metabolic activity: 58 patients had imaging reports to follow for their condition. The other 42 had no imaging or it was not applicable or relevant. Out of 58 patients, 36 patients (62%) had positive response in their scans after the treatments. In 17 patients the results were mixed or improved initially, or the tumor was stabilized (total response of 91%). Five cases (8%) continued to progress.

Decrease in VEGF/FGF-2/IL-8: 37 patients had increased VEGF, correlating with higher risk of metastasis. 34 patients had decreased VEGF after the treatments (92%). Three patients progressed despite therapy (8%).

Twenty patients had increased CTC. Sixteen patients had positive circulatory tumor cells response by lowered CTC, which correlates with both disease-free and overall survival posttreatment. One patient got worse and 3 had mixed responses (initially improved then progressed).

Since patients with cancer may have significant stratifying confounders in selecting their control group, we used each patient's preinterventional status as the control arm. Patients' other stratifying confounders did not change during the study.

1. These data reveal superior response in the group of patients compared with the controls (conventional therapies). In 62% of patients treated, there was no conventional treatment option available at the time of referral. In this group results were far better compared with conventional modalities of treatment.
2. Patients with stage IV terminal disease receiving the above program, improved beyond the standard-of-care expectations, and the patients who did receive chemotherapy concurrently with above targeted therapies had significant improvement in quality of life and chemotherapy response.

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Let's Talk About Sex: the Effects of Prostate Cancer on Sex, Men, and Their Relationships

by Daniel Lander, ND, FABNO

Sexual dysfunction is undoubtedly one of the most common long-term side effects of cancer and cancer treatment, yet it is still a topic that health-care providers shy away from. It has been shown that nearly all patients with cancer report some impact of cancer treatment on their sexual functioning; and when asked, half of all patients said that they desired additional care and support in the area of sexual health.[1]

In particular, the treatment of prostate cancer directly affects a man's ability to have an erection. Both radical prostatectomy and radiation therapies not only damage the cavernosal nerves but can also injure the penile arteries, causing local inflammatory changes and tissue hypoxia. If not corrected, these changes will lead to a loss of smooth muscle cells, an accumulation of collagen, and eventual permanent fibrosis of erectile tissues. Conversely, hormone-ablative therapies used in the treatment of recurrent and advanced prostate cancers result in a loss of erections from an absence of testosterone. Estimates of the incidence of erectile dysfunction (ED) following prostate cancer treatment vary widely, but likely up to 80% of men have some difficulty. It is important that men are explicitly made aware of this fact, as most overestimate their expected sexual functioning after treatment. In one study, men were found to have anticipated their sexual functioning to be 12% to 45% better than it actually was 1 year following prostatectomy. This unrealistic expectation was also found to be strongly related to their level of distress.[2]

Standard Management of ED

Very few men recover erectile function without intervention. There are several options available in the treatment of ED following prostate cancer treatment. Management usually involves the use of one or more erectile aids, including oral phosphodiesterase type 5 (PDE-5) inhibitors, vacuum erectile devices, alprostadil administered as an intraurethral suppository or as an intracavernosal injection, or penile prosthesis implants. Each has its own advantages and disadvantages, and no one method is right for everyone. Although the PDE-5 inhibitors are the most commonly used erectile aids, they generally have a low response rate with only one-third of men with prostatectomy-induced ED reporting functional erections after use.[3]

Naturopathic Approaches to ED

With very few exceptions, there has not been any research published on the use of natural therapies for the treatment of ED specifically related to prostate cancer treatment. However, it is worthwhile to briefly review the body of research that exists regarding the use of natural agents to improve erectile function overall, as these approaches can be helpful when used as part of a comprehensive management plan for prostate cancer treatment-induced ED.

Lifestyle Factors

In addition to not smoking and maintaining a healthy body weight, minimizing stress and regular exercise are important aspects of a comprehensive treatment plan for ED. The sympathetic nervous system is responsible for maintaining the penis in its flaccid state. Adrenaline is a very potent natural antierection chemical, and high serum levels associated with increased stress will undermine any treatment designed to improve erectile function. Stress management will therefore be the cornerstone of any integrative treatment of ED.

Physical fitness has long been known to be correlated with erectile function. Most notably, a study following men after completing radiation therapy for their prostate cancer found that active men had significantly better erectile function scores compared with inactive men.[4] Additionally, in men receiving androgen deprivation therapy, a 12-week exercise program successfully prevented a decrease in their sexual activity and libido compared with the men undergoing usual care alone.[5]

Acupuncture

A recent systematic review of the existing clinical trials studying acupuncture for the treatment of ED found that in addition to several positive uncontrolled trials, three out of four randomized controlled clinical trials demonstrated that acupuncture had a significant therapeutic effect compared to sham acupuncture.[6]

Nutritional Supplements

L-arginine, and its precursor L-citrulline, are converted in the penile endothelial cells to nitric oxide, which is required for proper erectile function. In addition to single agent studies, several clinical trials have also looked at the use of L-arginine combined with other substances such as a Pycnogenol and adenosine monophosphate, as these agents may work synergistically by also increasing nitric oxide production through stimulation of the enzyme nitric oxide synthase.[7–13] Additionally, a recent rat study showed that L-arginine administered after pelvic radiation prevented the accumulation of connective tissue in the penis by 18% and elastic fiber deposition by 61%.[14] Similarly, L-carnitine has also been shown to increase nitric oxide levels, and there is evidence suggesting that

PDE-5 inhibitors may be more effective if used in combination with acetyl-L-carnitine and propionyl-L-carnitine in men with ED following prostatectomy.[15]

Botanicals

There is a growing body of evidence to support the use of ginseng and yohimbine for the treatment of ED of various causes. A systematic review of seven randomized controlled clinical trials of Korean red ginseng root showed it to be significantly more effective than placebo in the treatment of ED.[16] Similarly, yohimbine has also consistently been shown to be more effective than placebo in clinical trials evaluating its use in the treatment of ED.[17]

Other botanical agents have not been the subject of as much study, but a single randomized controlled trial of maca root showed improved erectile function and psychological scores compared with placebo.[18] Additionally, a previous study demonstrated that maca supplementation improved libido in healthy men without altering serum testosterone levels.[19]

There have been two randomized clinical trials assessing the effectiveness of saffron on ED. The first, a crossover study with sildenafil failed to show an effect, but the second demonstrated a significant improvement over placebo in erectile function in men with fluoxetine-induced ED.[20,21] Similarly, the effect of tribulus on ED has also been studied with mixed results. Although it was not found to be effective as a single agent, a patented combination product of tribulus, an algae extract, and polymers of D-glucosamine and N-acetyl-D-glucosamine was shown to significantly improve several measures of sexual function in two randomized controlled trials.[22–24]

Although early studies with ginkgo showed benefit in selective serotonin reuptake inhibitor-induced ED, follow-up trials have shown no effect compared with placebo.[25,26]

A Few Words of Caution

When treating ED in men who have an active prostate cancer or those who are at high risk of recurrence, it is important to keep a few cautions in mind. In animal studies, high doses of L-arginine have been shown to stimulate the release of various growth factors, including growth hormone, insulin-like growth factor 1, insulin, and prolactin and a diet high in L-arginine compared to a control diet was shown to promote cancer growth in mice.[27] Additionally, tribulus has been shown to increase testosterone levels and bind testosterone receptors that could potentially support prostate cancer cell growth.[28] As such, the use of these natural agents, although they may be useful in improving erectile function, may not be appropriate for many patients with a history of prostate cancer.

The Emotional and Relational Aspects of Prostate Cancer and Treatment-Related ED

Despite the many interventions for erectile dysfunction, many couples report that they are dissatisfied with their sexual relationships and eventually cease engaging in sexual relations altogether. While the focus has largely been on improving erectile function, the sexual

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impact of prostate cancer treatment is multifactorial. Physically, many changes can occur after treatment in addition to ED. Depending on the therapies used, these may include decreased libido, loss of ejaculate fluid, penile shortening, climacturia, dysorgasmia, and body composition changes including the loss of muscle mass and gynecomastia. All of these can take a toll on a man's self-esteem and sense of masculinity. In fact, the diagnosis and treatment of any cancer can challenge several social and cultural definitions of masculinity, including physical strength, self-reliance, being a provider, and maintaining control. Additionally, sexuality itself is an important aspect of adult self-concept, and sexual function is often a key component of male identity. As such, men may need to renegotiate a new masculine identity following their diagnosis and treatment for prostate cancer.[29] This will inevitably have a significant impact on a man's sexual relationships, and it is important to remember that prostate cancer does not only affect the patient, but also greatly affects their partners' well-being. While this may seem obvious, it is all too often overlooked or dismissed as unimportant in the medical setting.

A great deal of suffering could be avoided though open and honest communication. However, this is often the first time a couple has needed to communicate about sexual issues. Without education and support around this, the necessary discussions often do not occur. Patients frequently feel embarrassed and try to avoid discussions regarding sex. Over time, this can lead men to withdraw physically and emotionally from their partners. When this happens, partners often feel abandoned, lonely, and isolated in the relationship. Specifically, communicating relational values between partners is especially important. Both men and women commonly overestimate the value that their partner places on physical pleasure compared with relational intimacy, yet it has been shown that the withdrawal of intimacy and affection, not coital sex, causes the biggest stress on a relationship.[30]

Three common traits were found among couples who successfully maintained satisfying sexual intimacy after prostate cancer treatment; namely, persistence, flexibility, and acceptance.[31] Just as men may need to renegotiate a new masculine identity following their diagnosis and treatment, couples may need to redefine what constitutes good sex. Couples can learn how to have satisfying sexual experiences whether or not an erection is possible. Although sex will often be different after treatment, it can definitely still be enjoyable.

Sexual health promotion is an important part of holistic medicine, and patients with cancer and their partners are clear in their desire to have more support from health professionals in this area. There are many options available in the management of ED, and naturopathic approaches may be important additions to a comprehensive treatment plan to maximize sexual rehabilitation during and after prostate cancer treatment. Although not always stressed, the sexual effects of prostate cancer affect both patients and their partners, and it is important for all health-care providers to reassure couples that even though prostate cancer treatment may impair sexual function, sexual activity and certainly relational intimacy need not end.

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The Concern about B Vitamins Affecting the Oxidant Effect of Intravenous Ascorbate for Malignancy

by Maiko Ochi, ND; James Hetherington, ND; and Davis W. Lamson, MS, ND

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Abstract

The use of intravenous ascorbate has a long history in complementary medicine. Its efficacy against malignant cells via a prooxidant mechanism has been previously demonstrated. In some quarters, B vitamins have been included with intravenous ascorbate therapy. Because of the antioxidant effect of some B vitamins, the question arose as to whether their presence could decrease the antimalignant effect of ascorbate. The data are summarized regarding the direct ability of several B vitamins to decrease the concentration of the active agent providing the antimalignant effect. The individual case of cobalamin in this regard is more complex than other B vitamins, in that cobalamin and ascorbate generate hydrogen peroxide and kill tumor cells in vitro. The implications of this result certainly warrant in vivo studies. The overall conclusion is that data do exist demonstrating that some B vitamins do have the capacity to decrease the concentration of the antimalignant agent from ascorbate at the tissue of concern. The authors recommend that B vitamins or other antioxidant materials not be included with intravenous ascorbate intended for anticancer purposes.

Introduction

There is adequate in vitro demonstration that ascorbate, at concentrations attainable in humans, can have a cytotoxic effect on malignant cells.[1,2] Intravenous ascorbate has been shown to benefit cancer patients.[3–7]

The proposed mechanism for the cytotoxic effect of ascorbate begins with the donation of an electron from ascorbate to molecular oxygen creating a superoxide radical anion, followed by conversion to hydrogen peroxide by several mechanisms. It is postulated that the initial electron transfer proceeds first to iron (III), which reduces to iron (II), which then transfers an electron to oxygen (see Figure 1, p. 98).[2]

Because of previous demonstrations of the antioxidant properties of several of the B vitamins, the question arises as to whether concurrent administration of B vitamins with intravenous ascorbate could be deleterious to the desired cytotoxic effect of ascorbate on malignant cells. Such concern was one factor leading to the Drisko-Khosh protocol for administration of intravenous ascorbate in the Program in Integrative Medicine at the University of Kansas Medical Center (ascorbate, magnesium chloride and sterile water). (See acknowledgement.)

The following sections cite data found on the interactions of certain B vitamins with superoxide or hydrogen peroxide, the intermediate agents believed chiefly responsible for the effect of ascorbate on malignant cells.

Thiamine – Vitamin B1

There are many publications on the antioxidant effects of thiamine under various conditions. The one most to the point at hand showed the scavenging ability of thiamine for superoxide (generated by the xanthine oxidase/hypoxanthine system) to be dose dependent and able to be driven to completion under the in vitro experimental conditions. It was suggested that thiamine was sacrificed to some extent in the course of scavenging reactive oxygen species (ROS).[8] A previous report demonstrated thiamine quenching of superoxide generated by pyrogallol autoxidation. It was also stated that no appreciable reaction of thiamine with hydrogen peroxide occurred, but no data were provided.[9]

Riboflavin – Vitamin B2

Direct and uncomplicated effects of riboflavin on hydrogen peroxide or superoxide in vitro were not able to be located.

Nicotinamide (Nicotinic Acid) – Vitamin B3

A 2000 publication referred to a 1969 report, which stated that nicotinamide had a high rate constant

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for reaction with superoxide (7×10^9).[10,11] However, a 1999 publication determined that nicotinamide did not scavenge superoxide generated in vitro.[12]

A 1995 report showed that superoxide generated by autoxidation of pyrogallol was quenched by nicotinic acid only at supraphysiologic concentrations. It was further stated that there was no appreciable reaction of nicotinic acid with hydrogen peroxide, but data were not provided.[9]

solutions were used for generation of superoxide and it was demonstrated that 1 mM P or pyridoxamine (PM) readily quenched superoxide to the range of 66% to 97%.[13] (Note: P, PM, and pyridoxal-5-phosphate [PP] are interconvertible in normal cells.)

Three publications after the 2001 report dispute the findings that P and PM inhibit superoxide radical generation. A 2006 report showed that in a system demonstrating reactions of superoxide, hydroxyl radical, and hydroperoxyl radical with organic molecules, superoxide radical did not react with P.[14] A 2008 report claimed that PM did not react with superoxide radical or hydrogen peroxide generated by albumin-Amadori intermediates.[15] A 2009 publication used an endothelial cell model to demonstrate whether preincubation with P, PM, or PP would inhibit superoxide generation from hydrogen peroxide. It was stated that only PP directly interacted with superoxide radical and that P and PM lowered superoxide by interaction with NADPH oxidase.[16]

When U937 cells (a human leukemic monocytic lymphoma cell line) were exposed to hydrogen peroxide, superoxide was produced. When the cells were preincubated with P, PM, or PP, superoxide was quenched in a dose-dependent manner. While the concentrations of P, PM, and PP were above physiologic levels, the authors concluded that vitamin B6 compounds could reduce damage due to ROS.[17]

Figure 1: Equations showing the generation of hydrogen peroxide via superoxide

Ascorbate anion can transfer an electron directly to an oxygen molecule forming the superoxide radical anion (O2–), or it can reduce Fe+++ to Fe++, which then transfers the electron to oxygen.

$$\text{Ascorbate anion} + O_2 \longrightarrow O_2^{-}\bullet + \text{Ascorbate radical}\bullet$$

Superoxide dismutase reacts with superoxide to produce hydrogen peroxide and oxygen.

$$2\,O_2^{-}\bullet + \text{Superoxide Dismutase} + 2H^{+} \longrightarrow H_2O_2 + O_2$$

Pantothenic Acid – Vitamin B5

Pantothenate was stated to have no quenching effect on superoxide generated by pyrogallol autoxidation until a supraphysiologic concentration of 3.0 mM was reached. However, the table provided in the publication showed a small effect at 1.0 and 2.0 mM, with no entry for 3.0 mM. It was further stated that pantothenate had no appreciable reaction with hydrogen peroxide.[9]

Pyridoxine – Vitamin B6

In 1995, there was a report of both pyridoxal and pyridoxine (P) quenching superoxide, "rather poorly" according to the rate constant of $10^3 M^{-1}s^{-1}$.[9] It was stated that no appreciable reaction with hydrogen peroxide was found. In a later 2001 study, high concentration glucose

Folic Acid – Vitamin B9

Folic acid was reported to have substantial scavenging ability against superoxide generated by the xanthine/xanthine oxidase system, to a degree comparable to that of the superoxide dismutase mimetic tempol.[18]

In 2000, it was shown that 5-methyltetrahydrofolate (5-MTHF), the main circulating folate in the body, directly scavenged superoxide generated by the xanthine/hypoxanthine system.[19] However, in 2006, a report disputed the 5-MTHF findings and claimed that 1 to 10 μM concentrations of 5-MTHF did not scavenge superoxide generated by the xanthine/xanthine oxidase system. Concentrations of 100 μM led to only modest scavenging of superoxide.[20]

Incubation of porcine aortic endothelial cells with 1 mM homocysteine and 0.5 mM folic acid or 5-MTHF for 24 hours prevented the homocysteine-mediated generation of superoxide radicals. The authors thought it unlikely that this effect was due to a reaction between homocysteine and folic acid or 5-MTHF, as it takes weeks for homocysteine levels to fall after folic acid administration. It was thought more likely that folic acid and 5-MTHF directly scavenged superoxide or prevented its generation.[21]

Cobalamin – Vitamin B12

It was reported that cobalamin had potent superoxide scavenging ability. In a cell-free experiment, cob(II)alamin (Cbl[II], an intracellular form of vitamin B12) was reacted with superoxide (generated by the xanthine oxidase-acetaldehyde system). There was rapid oxidation of Cbl(II) with generation of hydrogen peroxide. The resulting Cbl(III) can be reduced to Cbl(II) intracellularly. Cbl(II) also disproportionates to Cbl(III) and Cbl(I), the latter of which reacts rapidly with oxygen to produce

hydrogen peroxide. To elucidate the intracellular effect of a commonly used form of cobalamin, human aortic endothelial cells were preincubated with 100 nM cyanocobalamin for 24 hours. Superoxide generation by paraquat was prevented by the intracellular result of cyanocobalamin to the same degree as by superoxide dismutase.[22]

Hydrogen peroxide was rapidly produced by combination of 25 μM hydroxycobalamin and 500 μM ascorbic acid added to cell-free culture medium (containing nutrients including an iron salt). No peroxide was produced by hydroxycobalamin alone. Ascorbic acid alone produced about one-fifth as much peroxide.[23]

A similar accumulation of hydrogen peroxide occurred when hydroxycobalamin and ascorbic acid were added to human epidermoid larynx carcinoma cells (HEp-2). (Note: No hydrogen peroxide was produced by either of the two reactants alone.) Within 24 hours after addition of 25 μM hydroxycobalamin and 500 μM ascorbic acid, there was 90 to 95% cell death. Each of the agents alone produced no cell death.[23]

An earlier study looked at the combined effect of cobalamin with ascorbic acid on three ascites tumor cell types and found a synergistic effect decreasing mitotic counts and survival of tumor cells.[24] For completeness, it should be mentioned that a 1991 publication claimed that the previous report by the same authors of growth inhibition and death of ascites tumor cells by cobalamin and ascorbic acid was due in fact to dehydroascorbic acid, not ascorbic acid.[25] This concept was not discussed in the 2007 publication.[23,24]

Summary

Thiamine quenches superoxide, but not hydrogen peroxide. Data were not available to define these possibilities with respect to riboflavin. There are conflicting reports on the ability of nicotinamide to react with superoxide. Nicotinic acid at supraphysiologic concentrations is said to quench superoxide, with no appreciable effect on hydrogen peroxide. Pantothenate at supraphysiologic concentration also quenched superoxide, without effect on hydrogen peroxide.

In the group of vitamin B6 compounds, pyridoxal and P reacted poorly with superoxide according to one publication, with no reaction with hydrogen peroxide. In a later publication, 1 mM P or PM quenched superoxide extensively. Three even later publications disputed the reaction of P and PM with superoxide and reported a lack of reaction of P with hydrogen peroxide. It was stated that only PP reacted directly with superoxide.

Folic acid was claimed to react with superoxide comparably with superoxide dismutase. One study found that 5-MTHF also reacted with superoxide, but a later report disputed the finding and stated that 1 to 10 μm 5-MTHF did not scavenge superoxide, and that a concentration of 100 μm 5-MTHF gave only modest scavenging. One year later, 0.5 mM folic acid or 5-MTHF was reported to scavenge superoxide. Therefore, 5-MTHF's ability to scavenge superoxide may depend on concentration.

Cobalamin, in a cell-free experiment, was shown to rapidly quench superoxide and produce hydrogen peroxide. In the presence of oxygen, this became a cyclic reaction to convert all superoxide to hydrogen peroxide. In a cell culture experiment, 100 nM cyanocobalamin prevented detection of superoxide produced by a generation system. In cell-free culture medium, 25 μM hydroxycobalamin and 500 μM ascorbic acid rapidly

produced hydrogen peroxide. In studies on tumor cell lines, the combination of cobalamin and ascorbic acid produced hydrogen peroxide and had a synergistic effect in decreasing mitotic counts and survival of tumor cells.

Conclusions

It was mentioned above that the antitumor effect of high concentration ascorbate performs its function in the interstitial fluid beyond the blood circulation. Ascorbate is converted to superoxide, which proceeds to the hydrogen peroxide believed to be the active agent. Most of the B vitamins can quench superoxide under some conditions and would presumably lower the concentration of hydrogen peroxide available for antimalignant action. Therefore a caution seems appropriate against the inclusion of B vitamins with intravenous ascorbate aimed at tumor cell cytotoxicity. However, this general recommendation based on chemistry cited above needs the support of in vivo studies for certainty.

In the case of cobalamin specifically, the situation is more complex. As cobalamin and ascorbic acid can react in the intravenous reservoir bottle, it seems likely that less ascorbate would be delivered to the blood circulation when accompanied by cobalamin. It might appear a moot point as hydrogen peroxide results from the decreased ascorbic acid. However, it has been shown that almost all hydrogen peroxide in the systemic circulation is eliminated.[2] This occurs chiefly because the erythrocyte membrane is extremely porous to hydrogen peroxide and allows peroxide disposal by erythrocyte catalase. Therefore, it does appear that a reduced amount of ascorbate would reach the interstitial fluid, with relatively little hydrogen peroxide.

However, cobalamin and the remaining ascorbate would both arrive in the interstitial fluid. The previously mentioned reaction of cobalamin and ascorbate would generate hydrogen peroxide. So the obvious question becomes, does the presence of cobalamin in the interstitial fluid contribute more than the detriment of less ascorbate being present. This becomes a question of chemical kinetics. Will the presence or the absence of cobalamin with ascorbate provide the most positive effect against malignant cells in vivo? Existing in vitro studies show that cobalamin and ascorbate cause more tumor cell death than ascorbate alone. But no matter what measurements or calculations might be acquired to predict the interstitial concentration of hydrogen peroxide, with and without cobalamin, the bottom line is that in vivo studies are required before this question can be answered.

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Inositol Modulation of Essential Metabolic Pathways of Insulin Resistance in Metabolic Syndrome, Polycystic Ovarian Syndrome, and Type 2 Diabetes

by Cristiana Paul, MS, and David M. Brady, ND, DC, CCN, DACBN

This article will review the evidence for the abilities of myo-inositol (MI) and D-*chiro*-inositol (DCI) to improve dysglycemia and related characteristics of metabolic syndrome (MetS), type 2 diabetes (T2D), gestational diabetes, and polycystic ovarian syndrome (PCOS) by acting in critical metabolic pathways of insulin resistance (InsR).

1. Basic Facts About Inositols

Inositol occurs naturally as nine isomers in a variety of vegetarian and animal foods as well as in the human body. The two isomers MI and DCI have been recognized to be the most predominant and with important functions in human physiology. D-pinitol (a methylated form of DCI) also occurs in human tissues and in certain foods. See Figure 1 (p. 102) for details.

MI and DCI are components of intracellular signaling mediators of insulin action (see details in Figure 2, p. 102).[1,2] Most compelling research to date has been performed with the MI and DCI forms of inositol.

Only a few human studies have used the D-pinitol form and had mixed results. Orally administered D-pinitol was shown to be partially (approximately 33%) converted to DCI in the human body, but no clinical studies are available to date to show how its effects compare with those of MI and/or DCI supplementation.[2–5]

Inositol is not considered an essential nutrient in human nutrition, since MI and DCI can be synthesized in the human physiology from glucose. MI converts into DCI at rates that are specific for various types of tissues.[6] However, MI to DCI conversion has been found to be much lower than normal in patients with T2D or PCOS, as evidenced by their measurement in blood, tissues and urine. For example, one study assessed the urinary ratio of MI/DCI in various populations and the results were as follows[6]:

- 2.5 for control subjects;
- 20.4 for type 2 diabetic patients which may include PCOS patients;
- 13.2 for nondiabetic relatives of type 2 diabetes patients;
- 13.6 for type 2 diabetic patients.

The conversion of MI to DCI is achieved by an epimerase enzyme and its activity was observed to correlate inversely with the degree of insulin resistance.[6,7] Some researchers have categorized this epimerase downregulation as an "enzyme defect" associated with syndromes that display InsR. However, there are reasons to believe that this so-called defect may not simply represent a random genetic mutation but may be the result of evolutionary pressures for adaptation to variable food intake and survival, which selected genetic types more susceptible to developing InsR.[8–14] Thus, the downregulation of epimerase may be viewed instead as a genetically programmed metabolic switch meant to downregulate glucose utilization, thus favoring metabolism of fat for fuel. Specifically, epimerase inhibition results in the reduction of DCI produced from MI in various tissues, while intracellular glucose disposal is influenced by DCI derived cellular mediator DCI-IPG. Figure 2 depicts the intracellular roles of DCI-IPG. Thus, when DCI levels are lowered, glucose metabolism is impaired and this explains in part the state of InsR.[6]

Some researchers hypothesize that this adaptation may have occurred during an "evolutionary type of InsR" triggered by famine, in which case body fat stores release more free fatty acids (FFA). In contrast, the "modern type of InsR" often occurs in the setting of excess caloric intake, especially from fat and high body fat. However, these two distinct metabolic states are similar in the sense that they both display elevated plasma free fatty acids. Excess fatty acids have been shown to impair glucose disposal through well known metabolic switches, which can cause or aggravate InsR.[13,14]

2. MI and DCI Derivatives Alleviate Insulin Resistance

MI and DCI were revealed to be components of a large family of intracellular insulin-signaling mediators. These include phosphoinositol phosphates (PIPs) and inositol

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Inositol Modulation

Figure 1: Dietary sources and supplement forms available for inositols. Relevant inositol forms in human physiology and their interconversions.

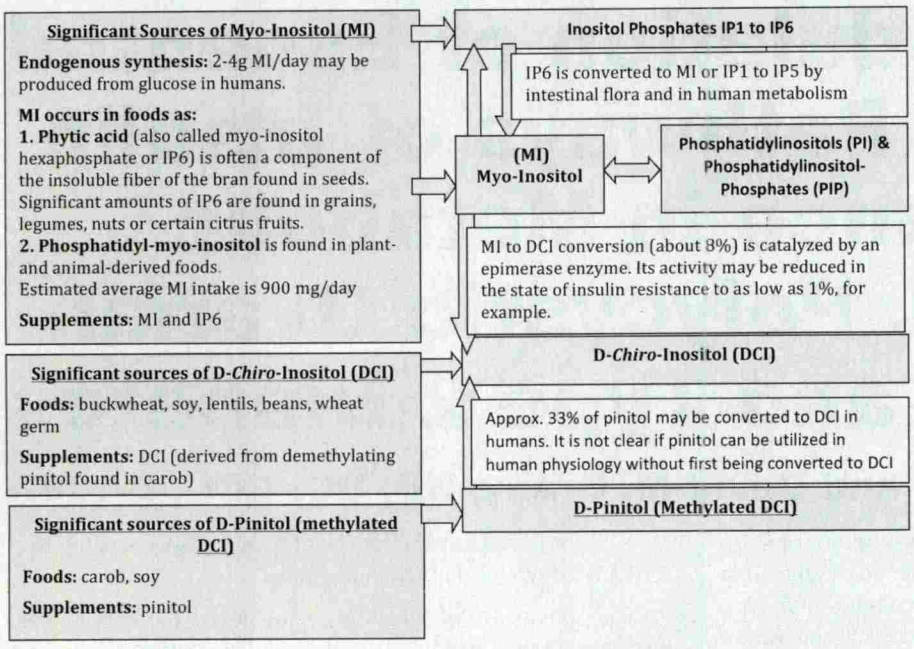
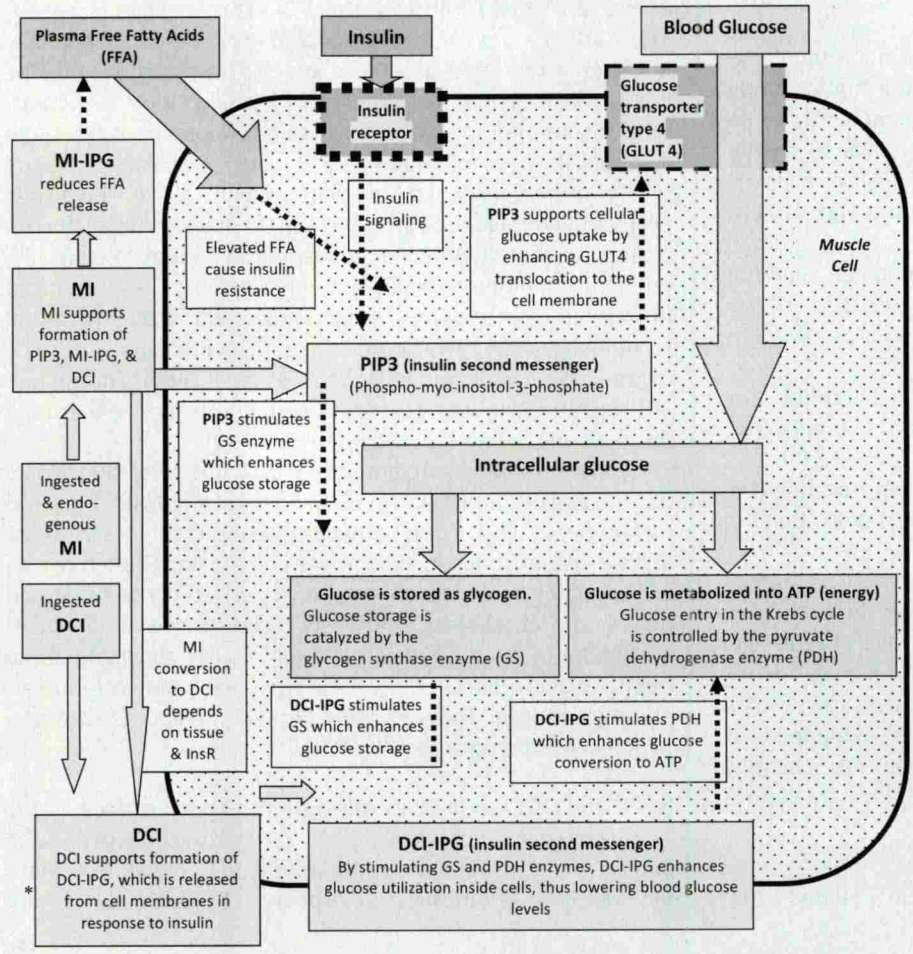


Figure 2: Roles of MI and DCI in supporting insulin stimulated glucose entry and its utilization inside cells.



phosphoglycans (IPGs; MI-IPG and DCI-IPG). The structure of DCI-IPG contains a methylated form of DCI and galactosamine, while that of MI-IPG contains MI and glucosamine and both types of IPGs contain Zn and Mn.[6,15]

Figure 2 illustrates the intracellular roles of MI and DCI derived mediators of insulin signaling for glucose disposal.[6,15–18]

Inositols and their derivatives support an improvement of glucose metabolism, as follows:

1. MI derived phosphoinositol-3-phosphate (PIP3) upregulates glucose transport inside the cells by stimulating GLUT4 translocation to the cell membrane.[15]
2. DCI derived DCI-IPG supports enhancement of glucose conversion to ATP by increasing its transport in the Krebs cycle. This is achieved by the stimulation of the pyruvate dehydrogenase (PDH) enzyme.[15,16]
3. MI and DCI derivatives PIP3 and DCI-IPG, respectively, increase glucose storage as glycogen inside cells. This is achieved by the stimulation of the glycogen synthase enzyme (GS).[7,15,16]
4. MI derivative MI-IPG supports downregulation of free fatty acids (FFA) release from adipose tissues by inhibiting the enzyme adenylate cyclase.[16] This effect is beneficial because FFA have been shown to impair glucose disposal, thus causing InsR and increased triglycerides synthesis.[19]

The four inositol mechanisms of action listed above tend to counteract some of the important metabolic deregulations occurring in InsR syndromes such as impaired glucose transport and insufficient cellular disposal along with elevated plasma fatty acids.[19,20]

In conclusion, researchers hypothesize that supplementation with MI and/or DCI is likely upregulating the production of MI-IPG, DCI-IPG, and PIPs in the body, and by doing so it is at least partially counteracting some of the metabolic deregulation specific to the state of InsR.[6,18]

Also, since MI to DCI conversion is impaired in individuals with InsR, it is important to always include DCI along

continued on page 104 ➤

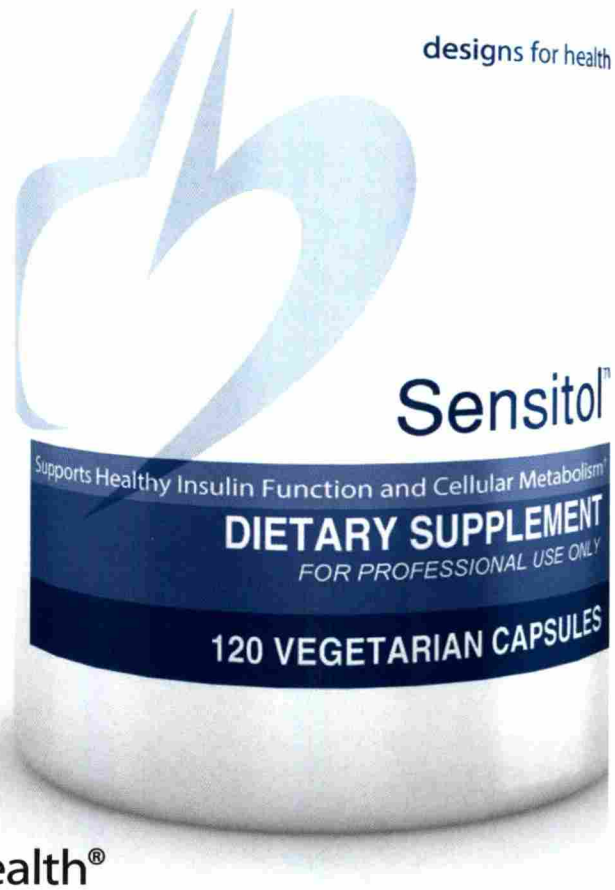
SENSITOL™

Supports healthy insulin function and cellular metabolism

Sensitol™ is a unique formulation comprised of two naturally occurring isomers of inositol – myo-inositol (MI) and D-chiro-inositol (DCI) – along with alpha lipoic acid, which support insulin function and the cellular metabolism of glucose, lipids, and hormones.

FUNCTIONAL BENEFITS OF SENSITOL™

- Supports glucose transport inside the cells
- Supports glucose conversion to ATP by increasing its transport in the Krebs cycle
- Supports glucose storage as glycogen inside cells
- Supports down-regulation of free fatty acids (FFAs) release from adipose tissues, which is beneficial because elevated FFAs have been shown to impair glucose disposal and increase triglycerides synthesis)



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➤ *continued from page 102*

with supplemental MI. Conversely, supplementing with DCI (or D-pinitol) alone cannot not fulfill the MI roles that are distinct from DCI, since DCI does not convert to MI.

Metformin is an insulin-sensitizing pharmaceutical drug and it is important to remark here that one of its mechanisms of actions involves the release of DCI-IPGs from cell membranes, making them available to participate as secondary messengers in insulin signaling. However, the efficiency of metformin's action may be dependent on having adequate DCI-IPG stores in the body, which were shown to be inadequate when InsR was present.[21–23] Thus, we hypothesize that supplementation with MI and DCI may be warranted in most patients that are prescribed metformin for glucose control.

3. Supplementation with Inositols Forms MI and/or DCI Alleviates InsR and Related Abnormalities of PCOS

Polycystic ovary syndrome and its characteristic physiological imbalances. PCOS is characterized by hyperandrogenism, oligoanovulation, and oligomenorrhea and has been reviewed extensively by P. W. Smith in the May 2014 issue of the *Townsend letter* and by Saha, Marshall, and Murray.[24–26] Many researchers consider PCOS a subset of MetS with exaggerated InsR and additional dysregulation of sex hormones affecting 5% to 10% of women.[8–11] PCOS was also referred to as "Syndrome XX," since it is a more severe form of Syndrome X or a phenotypical subset of T2D.[1,24,25,27,28]

Women with PCOS are more susceptible to display elevated insulin levels and to develop MetS with its associated comorbidities.[27,28] Hyperinsulinemia occurs in approximately 80% of obese PCOS women, as well as in 30% to 40% of lean PCOS women.[1,29] PCOS women tend to have 30% to 40% lower glucose disposal than weight-matched normal controls.[28] One cause of the exacerbated InsR in PCOS is believed to be due, at least in part, to a number of postinsulin receptor signaling alterations which affect glucose transport and its cellular metabolism.[30–32]

Since PCOS often involves genetic polymorphisms on insulin signaling pathways, it will likely manifest with InsR in all phases of a woman's life. For example, for PCOS women in menopause the syndrome manifests as an exacerbated state of InsR and displays an above average risk of obesity, metabolic syndrome, diabetes, and cardiovascular disease.[33]

A syndrome similar to PCOS is believed to affect men who are relatives of women with PCOS with the same 5% to 10% incidence as in women. PCOS-specific genes are inherited as an autosomal inherited trait (not related to the sex chromosomes). Men with PCOS genetics have similar hormonal patterns as PCOS women (elevated androgens and low SHBG) and – more importantly – a similar exaggerated state of insulin resistance and risk of cardiovascular diseases. This type of male syndrome is often associated with early onset baldness in the 20s.[34,35]

Summary of Studies that Used MI and/or DCI for PCOS.

Since 1998 numerous studies have been published which investigated the potential for MI and DCI to alleviate the main physiological imbalances of PCOS: infrequent ovulation, oligomenorrhea, elevated androgens, and hyperinsulinemia, a manifestation of InsR.

Table 1 includes a listing of the results from the most relevant studies that used either MI or DCI alone, or a combination of both for alleviating PCOS. All MI and/or DCI interventions achieved significant improvements in the PCOS characteristic deregulations. Ovulation and menstrual regularity were restored in a significantly higher percentage of women in the treatment groups. Total and free testosterone levels were significantly lowered in all studies that measured it (see Table 1). One study also showed improvement in LH and LH/FSH ratio.[36]

All 10 inositol interventions summarized in Table 1 achieved dramatic reductions in homeostatic model assessment of insulin resistance (HOMA-IR), while 5 studies reported impressive lowering of insulin (area under the curve [AUC] post glucose load) and glucose (fasting and/or AUC post a glucose tolerance test).

The dyslipidemia markers (triglycerides, HDL, total cholesterol) were reported in 6 of the studies listed in Table 1 and all show statistically significant improvements. Most dramatic changes were observed in triglyceride lowering, while notable improvements were also seen for HDL, total cholesterol and blood pressure.

Most studies have investigated either DCI or MI for PCOS interventions, but it is not clear why researchers chose one form over the other in any particular study. Two studies tested a combination of MI + DCI (the equivalent of 3300 mg MI + 84 mg DCI in powder form), while 1 of them compared the effects of this combination with that of 4g MI alone (see results in Table 1).[27,37] After 6 months of treatment, both MI and MI+DCI groups showed improvement in all the measured metabolic parameters. However, the MI + DCI combination reduced HOMA-IR twice as much with the rest of the results also superior to those obtained in the MI alone group. It is interesting to note that the results obtained at the end of the study (after 6 months) were significantly better than at midpoint (after 3 months), which implies that MI and/or DCI interventions needed some time to realize their full potential.

The rationale for using the MI + DCI combination was stated by the study authors as follows: "Both myo-inositol (MI) and D-chiro inositol (DCI) glycans administration has been reported to exert beneficial effects at metabolic, hormonal and ovarian level. Beside these common features, MI and DCI are indeed different molecules: they belong to two different signal cascades and regulate different biological processes."[37] This concept is also substantiated by the distinct metabolic roles of MI versus those of DCI and their respective derivatives as outlined in Section 2 and Figure 2.

One recent study showed that interventions with 4 g/d MI or 1 g/d DCI yielded very similar results in parameters measured such as improved ovulation, HOMA-IR, androgen levels, and blood pressure (see Table 1).[38] This may be explained by the fact that the 4 g/d doses of MI could possibly push the conversion of MI to DCI to an extent that may correct the DCI deficiency, at least in part. So, from this study alone one could conclude that DCI is 4 times more potent than MI in alleviating certain PCOS symptoms.

Larner authored many studies investigating and reviewing DCI, and he proposes that this is the more potent form of inositol for alleviating InsR.[6,16,18] On the other hand, MI is needed for oocyte quality and maturation. Concerns have been expressed by some researchers regarding supplementation with DCI without MI, since it may cause an MI deficit in the ovary.[7]

Overall, the MI doses used in studies ranged from 2 to 4 g/day, while a meta-analysis study of MI for PCOS concluded that the higher dose of 4 g/d seems to achieve much better results than lower doses in a higher percentage of subjects. Also, the benefits of inositol supplementation seem to correlate inversely with body fat, prompting researchers to speculate that obese patients may need and benefit from higher doses than 4 g/d.[29] Inositols compete with glucose for entry in the cells, so high blood glucose levels may require increased amounts of inositol.

Many of the MI, DCI, and MI + DCI interventions presented in Table 1 showed a trend for enhancing weight loss as evidenced by small but statistically significant reductions in BMI, while some also showed a reduced waist/hip ratio, an indication of reducing abdominal fat. Intra-abdominal fat generates inflammatory cytokines and contributes more to plasma free fatty acids than subcutaneous fat stored in the rest of the body. Plasma free fatty acids and inflammation are contributing factors to insulin resistance.

4. Supplementation with Inositols Alleviates Characteristic Abnormalities of MetS

The metabolic syndrome has been defined by "resistance to insulin-stimulated glucose uptake occurring in approximately 25% of the population at large" and association with a number of conditions known to be risk factors for coronary heart disease and diabetes.[39–41]

Supplementation with MI, or a combination of MI + DCI, has been proved to alleviate many aspects of MetS in postmenopausal and pregnant women. See Table 2 (p. 106) with results from four studies that have tested the effects of MI or MI + DCI supplementation on improving various metabolic markers of MetS.[42–45] Three of the studies described in Table 2 have reported dramatic drops in HOMA-IR, fasting insulin, ➤

Table 1: Summary of Main Intervention Studies with MI and/or DCI for Women with PCOS

		Markers of insulin resistance or sensitivity						Markers of CVD health					Weight		Androgens	
	Daily Dose	Gluc /IRI	HOMA-IR	AuC Insulin	Fasting Insulin	AUC Glucose	Fasting Glucose	Trigly-cerides	HDL	Total Chol.	DBP	SBP	BMI	WHR	Total Test	Free Test
PCOS Obese, 8 wks[53]	1200 mg DCI	–	–	–62%	–37% but NS	–8% but NS	NS	–40%	NS	–8%	–4%	–3%		–2%	–32%	–55%
	Placebo	–	–	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
PCOS lean, 8 wks[54]	600 mg DCI	+84% Insulin Sensitivity	–	–36%	–	–17%	–7%	–52%	–	–19%	–7%	–3%	–	–	–66%	–73%
PCOS, 14 wks[55]	4g MI + 400 mcg FA	–	–	–	–	–	–	–	+5%	–	–	–	–2%	–	–	–
PCOS, 12 wks[56]	4g MI + 400 mcg FA	–	–80%	–35%	NS	–16%	NS	–5%	–	–19%	–3%	–7%	NS	–	–72%	–72%
	Placebo +400 mcg FA	–	–13%	–2%	NS	no change	NS	–1%	–	+5%	+2%	+5%	NS	–	–6%	–4%
PCOS, 6 mo[37]	equivalent to 3300 mg MI + 84 mg DCI		–44%	–38%	–28%	–38%	–12%	–	–	–	–9%	–2%	–2%	–2%	–66%	–73%
	4g MI	–	–21%	–36%	–22%	–32%	–11%	–	–	–	–6%	–2%	–1%	–1%	–59%	–72%
PCOS, 6 mo[27]	equivalent to 3300 mg MI + 84 mg DCI	–	–40%	–	–18%	–	–16%	–13%	+8%	–14%	–	–	–	–	–	–
PCOS, 6 mo[38]	4g MI + 400 mcg FA	+76%	–50%	–	–	–	–	–	–	–	NS	–8%	NS		–36%	–22%
	1g DCI + 400 mcg FA	+81%	–49%	–	–	–	–	–	–	–	NS	–7%	nS		–33%	–23%
PCOS, 6 mo[57]	1g DCI + 400 mcg FA	+80%	–49%	–	–	–	–	–	–	–	NS	–7%	NS		–33%	–24%
PCOS, 12 wks[36]	0.5g DCI and no diet	+43%			–23%		–11%						–5%		–38%	
PCOS, 12 mo[58]	4gMI + NAC + 400 mcg FA	–	–51%		–45%		–12%									

➤

and fasting glucose, which were more pronounced than in the "placebo + diet" group.[42–44] The fourth study reported only improvement in fasting glucose.[45] Cardiovascular risk markers improved dramatically as well in all four studies. Also to be noted in the MI intervention groups is the enhanced weight loss versus the diet-only groups.[42–44]

The addition of lipoic acid in the study by Capasso may be justified by the following facts[44]:

- Lipoic acid supplementation has been found to increase the insulin sensitivity by about 20% to 30%.[46,47]
- Lipoic acid is a cofactor for the PDH enzyme.[46] Since DCI-IPG is also a cofactor of the PDH enzyme, this further supports the possibility that these two endogenous metabolites may act in synergy and in a complementary way to boost the activity of PDH, which in turn supports the conversion of glucose to energy.

Supplementation with 4 g MI was also shown to reduce the risk of developing gestational diabetes in PCOS women in three studies.[48–50] For example, D'Anna et al. supplemented pregnant PCOS women with 4 g MI and found that the incidence of gestational diabetes in the MI group was 17.4% versus 54% in the control group.[18] In another study, where MI + diet was used to treat gestational diabetes, there was a significant improvement in HOMA-IR of −50% versus −29% achieved in the placebo + diet group.[50]

D-*chiro*-inositol was administered to STZ diabetic rats and rhesus monkeys and shown to decrease hyperglycemia and enhance glucose disposal regardless of sex.[18] No human studies have been published so far to investigate MI or DCI for benefiting T2D, but all the evidence presented in this review supports the idea that MI and DCI supplementation may be beneficial for these patients by improving insulin sensitivity.

Pinitol, the methylated form of DCI, was tested in a few human studies using participants with T2D. The results are inconsistent and especially disappointing for obese diabetic participants.[2–5] It seems that approximately 33% of pinitol is converted to DCI in the human body, and it is not clear whether it needs to be in order to be beneficial or utilized in human metabolism. It is difficult to compare the effectiveness of pinitol with MI and/or DCI because these have been tested in different types of populations and not side by side in comparative studies.

5. Considerations for Optimal Dosing of MI and or DCI for Alleviating InsR in PCOS and MetS

Based on the studies reviewed above the 4 g MI dose, and doses ranging from 500 mg to 1200 mg of DCI, seem to be effective in alleviating InsR and the related metabolic derangements in PCOS, MetS, and gestational diabetes.

Individuals with PCOS or diabetes have a significant DCI deficiency in various tissues (liver, muscle, kidney, blood) compared with normal individuals, so it makes sense to supplement them with a dose of DCI comparable to the ones used in studies so far. However, one study showed that a safety threshold for DCI supplementation in PCOS patients may be set at 300 mg DCI/day, the highest dose that will not reduce oocyte maturation.[64]

Based on the pharmacokinetics of supplemental inositol, it makes sense to split the daily dose and provide half of it, every 12 hours, in order to maintain continuous therapeutic levels of inositols. It is best to take inositols on an empty stomach, especially away from meals high in carbohydrates, since inositol competes with glucose for absorption in the gut and uptake from the bloodstream into cells.[21,22]

Patients should make sure that they have adequate intake of zinc, manganese, and magnesium, as these minerals have an important role in inositol transport and metabolism. Other supplements, such as lipoic acid and NAC, may have additive synergistic effects in improving glucose metabolism.[44,46,47,51,52]

In conclusion, MI and DCI may be deemed conditionally essential nutrients for conditions such as MetS, T2D, and PCOS wherein dysglycemia and InsR play critical roles. The results of the clinical studies discussed in this review show that average dietary inositol intake and endogenous inositol production need to be supplemented with additional MI and DCI in order to bring their glucose metabolism closer to homeostasis.[27,36–38,53–58] This concept is also supported by the excess urinary loss of MI observed in these conditions. Thus, MI and DCI qualify as ingredients for medical foods in support of PCOS, MetS, gestational diabetes, and possibly also T2D.

For example, a dietary supplement is offered commercially by Designs for Health Inc., under the name Sensitol, which provides an inositol supplement composed of MI, DCI, and lipoic acid.

Table 2: Summary of Studies with MI for Metabolic Syndrome in Postmenopausal and Pregnant Women

		Markers of insulin resistance			Markers of CVD health					Weight loss		
	Daily Dose	HOMA-IR	Fasting Insulin	Fasting Glucose	Tri-glycerides	HDL	Total Cholesterol	DBP	SBP	BMI	Waist Circumference	WHR
Women postmenopausal n = 80, 6 mo[42]	4 g MI + diet	−77%	−69%	−17%	−21%	+28%	−20%	−12%	−4%	−3%	−6cm	–
	placebo + diet	−25%	NS	−4%	NS	NS	−7%	no chg	NS	−1%	−1cm	–
Women postmenopausal n = 80, 12 mo[43]	4 g MI + diet	−78%	−70%	−15%	−34%	+21%	−22%	−16%	−7%	−5%	−7cm	–
	placebo + diet	−42%	−33%	−6%	−9%	+5%	−10%	−9%	−1%	−2%	−1cm	–
Women postmenopausal n = 155, 6 mo[44]	4 g MI + lipoic acid + low-cal diet	−33%	−45%	−10%	−19%	+15%	−5%	–	−5%	−2cm	−9%	
	placebo + diet	−1%	no change	−5%	no chg	no chg	no chg	–	–	−3%	−1cm	−9%
Healthy pregnant women with MetS, n = 65, 60 days[45]	2 g MI + 800 mg DCI +10 mg Mn + 400 mcg FA	–	–	−4%	−24%	−10%	−20%	ns	−5%	–	–	–

In conclusion, human clinical trials using MI and/or DCI supplementation have only employed menopausal women with InsR, women of reproductive age with PCOS, and pregnant women at risk of gestational diabetes or those who have already developed it.

However, based on all the evidence available and mechanisms of action, it is reasonable to believe that MI and DCI may also improve glucose metabolism in most women with InsR or T2D of reproductive age regardless of PCOS status. The same rationale leads us to believe that most men with InsR as part of MetS or T2D may similarly benefit from MI and/or DCI supplementation. Men related to women with PCOS, who are likely to have PCOS type genetics, may benefit from these interventions even more so.

Individuals with dysglycemia, InsR, and diabetes tend to have elevated urinary excretion of MI, while that of DCI is typically reduced.[6,21,22] Excessive urinary loss of inositols may be due to elevated blood glucose which competes with inositols for reabsorption in the kidneys.[22] All studies report consistently that these individuals have an elevated urinary MI/DCI ratio, which may be due in part to a poor MI to DCI conversion. Each patient may have a different genetic and metabolic situation, while their diet and degree of obesity also influence their degree of InsR and thus MI/DCI ratios in various tissues. If the measurement of plasma and urinary MI and DCI become commercially available, it may be then feasible to optimize MI + DCI supplementation based on the ongoing needs of individual patients and on objective testing in the clinical setting. In fact, the urinary MI/DCI ratio has been proposed as an index of InsR by many research groups.[59–63]

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Inositol Modulation

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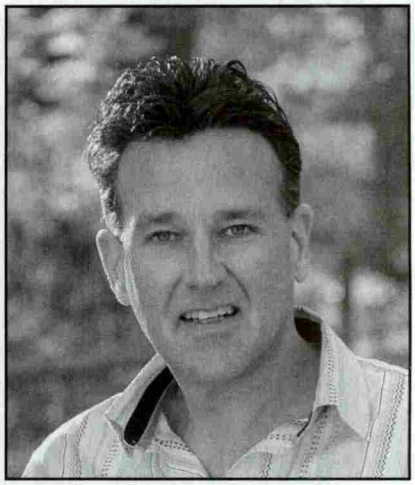

Dr. David M. Brady has over 23 years of experience as an integrative physician and over 19 years in health sciences academia. He is a licensed naturopathic medical physician in Connectucut and Vermont, and a dual-board-certified clinical nutritionist and received his original clinical training as a chiropractic physician. He currently serves as the vice provost for the Division of Health Sciences, director of the Human Nutrition Institute, and an associate professor of Clinical Sciences at the University of Bridgeport in Connecticut. He maintains a private practice, Whole Body Medicine, in Fairfield, Connecticut. Dr. Brady is also the chief medical officer for Designs for Health Inc. and Diagnostic Solutions Laboratory LLC. He is an internationally sought-after presenter and has appeared on the plenary speaking panel of some of the largest and most prestigious conferences in the field. Dr. Brady has published a multitude of peer-reviewed scientific papers and textbooks related to chronic pain, autoimmunity, and functional gastroenterology and is a featured contributing author in the medical textbooks *Advancing Medicine with Food and Nutrients* 2nd ed. (Kohlstadt I, CRC Press, Boca Raton, Florida; 2012), *Integrative Gastroenterology* (Mullin G, Oxford Press, Weil Integrative Medicine Library, New York, New York; 2011), and *Laboratory Evaluations for Integrative and Functional Medicine* 2nd ed. (Bralley JA, Lord RS, Metametrix Institute. Duluth, GA. 2008). His latest popular book is titled *Dr. Brady's Healthy Revolution: What You Need to Know to be Healthy in a Sick World*. You can learn more at DrDavidBrady.com.

Breast Cancer: These Natural Solutions Could Save Your Life

by Gary Null, PhD

Despite tens of millions of dollars invested into breast cancer research every year, tens of thousands of women will die from this devastating disease. Lifesaving solutions don't start with drugs and poisonous treatments; they start with prevention. Prevention is not walking, bike-riding, or purchasing a product for the cure; rather, it is an honest discussion about what causes inflammation and gene alteration in our bodies; that's where our journey towards breast cancer healing begins.

Breast cancer remains the leading cause of death and most commonly diagnosed cancer in women.[1] Breast cancer research is consistently one of the most highly funded cancers researched, yet each year it is estimated that over 220,000 women in the US will be diagnosed with breast cancer and more than 40,000 will die.[2] A natural diet and lifestyle adjustments can empower women and prevent them from being victims of breast cancer.

Diet and Lifestyle

Women in our culture have notably high instances of breast cancer. This implies that cultures that eat less fat, especially less animal fat, have the least breast cancer. The answer is really clear. Eat a lot of vegetables, fruits, whole grains and beans. Those foods provide protection.

Along with diet, prescription medications and synthetic hormones greatly influence our country's high breast cancer rate. This month, studies have shown that cholesterol-lowering drugs called statins can increase risks for invasive lobular carcinoma (the second most common type of breast cancer) by up to 143% in women diagnosed with hypercholesterolemia.[3]

Multiple epidemiological studies have looked at the relationship between a person's lifelong eating pattern and the development of cancer. Those studies have shown that the more vegetables and fruits a person eats, the less likely s/he is to develop cancer. People who eat 6 to 7 servings of vegetables a day plus 3 to 4 servings of fruit have the lowest risk.

Certain foods are medicinal in their ability to protect against breast cancer; for example, the isoflavones and phytoestrogens found in soybeans, soy products, and lima beans protect against cancer. A low incidence of breast cancer among Japanese women is largely attributed to a diet consisting primarily of soybeans, miso, tofu tempeh, green and black tea, sea vegetables, fish, whole grains, and fruit.

Other cancer-fighting foods include flax, fish high in omega-3 fatty acids (salmon, tuna, sardines, mackerel, and herring), cruciferous vegetables (broccoli, cauliflower, and brussels sprouts), mushrooms (reishi, shiitake, and maitake), and onions.

New research conducted by Dr. Luis Cisneros-Zevallos even suggests that peaches inhibit breast cancer metastasis and have chemical compounds capable of killing cancer cells.[4]

Along with these foods, herbs and supplements can also aid in your preventative plan. Herbs such as black cohosh, chasteberry, red clover, and turmeric are high in phytoestrogens. Phytoestrogen tricks the body into thinking that it's getting estrogen, but the advantage of phytoestrogens is that they tell the body to lower its own estrogen production, which helps balance your estrogen levels.

Some other herbals to know about are:

Cat's claw
Evening primrose, borage, and blackcurrant seed oils
Xiao Yao Wan (Chinese classic herbal formula)
Dandelion
Astragalus
Rosemary
Mint

Alternative Treatment Approaches

The daily protocol found below of vitamins and minerals is encouraged by Dr. Steven Rachlin, an internist in Syosset, Long Island, New York. Vitamins and minerals are a critical part of breast cancer prevention. Recent studies at Thomas Jefferson University show that retinoic acid, a derivative of vitamin A, has been proven to turn precancer cells back to healthy breast cells.[5]

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Emulsified vitamin A (up to 50,000 IU)
Beta-carotene (up to 100 mg)
Vitamin B1 (100 mg)
Vitamin B6 (100 mg)
Folic acid (3200 mcg)
Vitamin C (up to 5 g)
Coenzyme Q10 (400 mg)
Flaxseed oil (1 tbsp)
Cat's claw (300 mg)
Melatonin (up to 10 mg)
Pycnogenol (150 mg)
Pancreatic digestive enzymes (up to 40 g)
Aloe vera juice (9–12 oz)
Minerals

Enzymes

Enzymes are organic substances that help create reactions in the body, such as breaking down fats. They are linked to all the bodily functions that we need to live and stay well. There are 3000 enzymes in the body. A healthy person can produce enough enzymes to fight off cancer cells, but substances such as free radicals from smoke, pollutants, junk foods, and medications interfere with enzyme production.

Numerous studies link enzymes and breast health. More than 90 were conducted by universities throughout the world regarding the beneficial effects of enzymes. Much of this work has been done in Germany.

Exercise

Regular exercise is an important component of any prevention and treatment plan. Dr. Michael Schachter notes, "Any activity that removes accumulated toxins in the breast reduces the chance of women developing breast cancer. Studies show that aerobic exercise is associated with decreased cancer risk, as exercise promotes lymphatic drainage and sweating helps remove toxins from the tissues."

A study conducted at Helsinki University's Department of Oncology concluded that participating in a tailored exercise group for breast cancer survivors helped patients gain a sense of mastery, restoring their self-esteem and constructing a meaning for their cancer experience and its impact on their lives.[6]

Massage

Lymphatic detoxification is aided by manual lymphatic drainage (MLD), a simple method of massage that uses light, slow rhythmic movements to stimulate the flow of lymph in the body. This is especially important for women suffering from lymphedema, a condition that often occurs after a mastectomy: When our lymph nodes are not functioning properly or have been irradiated or removed, an excessive accumulation of stagnant waste occurs. The lymph system becomes overloaded, thus forming lymphedema.

MLD should be applied directly after surgery rather than when a massive edema has formed. This will guard against any possibility of a blockage in the system or alleviate any that exists. Studies in Europe show that severed lymph vessels regenerate with constant MLD therapy. The therapy makes the scars from the mastectomy more subtle, which increases the mobility of the arm. It also lessens pain from surgery and the uncomfortable sensitivity that occurs.

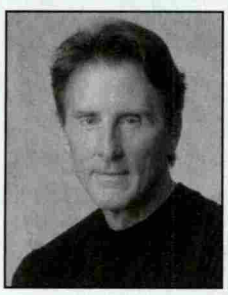
The Mind-Body Connection

Emotions drive healing systems, and the imagination and standard counseling can be used to increase a patient's will to live.

"I would like to give an example of a patient I have worked with for more than 20 years," said Dr. O. Carl Simonton, medical director of the Simonton Cancer Center in California and coauthor of *Getting Well Again* and *The Healing Journey*. "This 36-year-old woman came to me with metastatic breast cancer that had spread to her ribs and spine. Her father was a physician, and her husband's family had run a retail store for three generations. She was involved in helping her husband run the family business.

"Her religious and spiritual life was important to her. It was a great source of strength. She wanted more time to be involved in religious administration and spiritual counseling. As she began to pursue these areas, her beliefs about how she should be the good daughter, the good wife, and the good mother came into play. These beliefs were all quite rigid, allowing virtually no freedom for her own creativity. Over time we helped her make a shift in these beliefs and behaviors that was central to her recovery.

"She has been free of disease for 15 years. Currently, she is weller than well and runs marathons. The family store burned down about 10 years ago. Now she works primarily in church administration, doing religious and spiritual counseling, which is what she always wanted to do."



Gary Null is the host of the nation's longest-running public radio program, the *Gary Null Show*, and founder of the web-based Progressive Radio Network. A journalist and *New York Times* best-selling author who has written over 70 books on nutrition, health, and sociopolitical issues, Gary has received critical acclaim as director and producer of multi-award-winning documentaries, most recently *Death by Medicine* (2011) and *Knocking on the Devil's Door* (2011).

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Dietary Supplements: Concern and Opportunity

If you watch the news, you've probably noticed the increase in negative media about dietary supplements and integrative health care. If you don't watch the news, here are some of the recent highlights:

In early February, the New York State attorney general (NYAG) went after four retailers (Walgreens, Walmart, Target, and GNC). The NYAG stated that DNA bar code (DNAB) testing revealed that these retailers failed to show the correct herbs in their products. The NYAG has since refused to release its data or methods, and follow-up testing performed by GNC as well as outside labs using FDA-approved methods (primarily HPTLC) revealed that the products contained the stated ingredients. (Without getting into too much science, the products tested were extracts, which you wouldn't expect to contain whole plant parts anymore, so it's not surprising to not find DNA). GNC has been allowed to return its products to store shelves and also settled with the NYAG, including an agreement to perform DNA testing on ingredients moving forward.

Meanwhile, the NYAG convinced 13 other state attorneys general to sign a letter to Congress asking it to investigate. Two senators reached out to the FDA for comment. The FDA's response included the following statement, "Currently, if the FDA were to use DNA methods on botanical extracts, we would use them in combination with established chemical or other acceptable methods historically used to verify the identity of these products. At this time, the FDA does not use DNA sequencing by itself to analyze an herbal extract for phytochemicals." That reads to me like a politically correct way of saying, "We wouldn't use DNAB." At this time, it doesn't appear that Congress plans to take any action on the letter, but it has triggered a media firestorm and brought concerns about supplement quality to the limelight.

In addition to the NYAG actions, we've seen many other stories in the media this spring, including an attack on Dr. Oz, an enormous discussion and legislative push to eliminate parental choice with regard to vaccination (and accompanying criticism of doctors who allow parents to make that choice), and studies showing ineffective clinical impact of dietary supplements, often based upon a single study taken out of context of an entirety of research. Just yesterday, CBS.com ran a sensational story with the headline "Dietary Supplements Linked to Increased Cancer Risk." Further research with CBS revealed that this report was not even based upon a published study, but rather arose from discussion at a recent cancer meeting.

I don't believe that this barrage of media will stop.

We need to join together and take action to counter this incomplete, often misleading, and sometimes outright inaccurate barrage. I know that most of us are very busy and have our heads down in our clinical practices, but your practice (and your career) could be at risk if this trend continues. There are some large, ongoing public myths around integrative medicine and supplements, and it's critical to speak and ensure that the truth is told – and that the real facts get equal treatment in the media! Your patients, your communities, and your local legislators and regulators need to understand that dietary supplements are regulated. There are laws and regulations that clearly define how supplements must be manufactured, and the FDA has oversight to enforce this law. Furthermore, it's important to talk with your preferred supplement brands and let them know how critical clean, effective products are to our practices, and ultimately to our reputation as integrative practitioners as a whole. Encourage them to speak out and explain what they do to ensure a quality, properly labeled product.

It's essential that we speak as a loud and unified voice to teach consumers and regulators alike the value of integrative practitioners in the health-care system. *And we need to do it now* in order to ensure that our patients continue to have a choice when it comes to their health care.

Jaclyn Chasse, ND

Dr. Jaclyn Chasse is a practicing naturopathic physician in New Hampshire and medical director for Emerson Ecologics, where she oversees the Emerson Quality Program (EQP) and adherence to FDA and FTC regulations.

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Changing the Way the World Detects Cancer

by Jenny Hrbacek, RN

The typical annual physical in the US might include a mammogram, Pap test, or PSA count. These tests screen for reproductive cancers only. Occasionally, a colonoscopy may be ordered which looks in the large intestine but does not examine the small intestine, where cancers can also develop.

By the time a mammogram, for example, can pick up a breast cancer, it is often far enough along that the patient is immediately whisked into surgery, chemotherapy, and/or radiation. Screenings are not the same as prevention. In some circles, screenings are described as "trolling for business" because they are not sensitive enough to offer true early detection for prevention.

Yet true early detection tests exist and are readily available, if patients know to ask for them. These tests are much more sensitive and can detect cancer years before the lump or bump is diagnosed by more common means. These tests also detect a wide range of cancers. Depending upon the test, they can give an early warning for kidney, bladder, thyroid, uterine, and brain cancers; non-Hodgkin's lymphoma; pancreatic cancer; leukemia; and more.

One of the ironies of human nature is that we tend not to change our ways until we have to. An early warning that cancer cells are circulating in their bloodstream can be the incentive necessary for people to change their diet and work with an integrative practitioner who can establish a preventive protocol – perhaps intravenous vitamin C with Poly-MVA, and the use of curcumin or metformin to address cancer stem cells.

The more sensitive cancer tests available also play a big role in managing the posttreatment patient. Cancer patients who have completed their standard regimen of surgery, chemotherapy, and radiation need to know if their cancers are receding or growing. Typically after treatment, oncologists use standard tumor marker tests. If an elevation is seen with a tumor marker, a PET scan is ordered. The patient is subjected to carcinogenic radiation and the test results are often used to justify starting treatment again. Now the cancer is usually more aggressive and harder to treat.

The real danger of a repeat episode of cancer is metastasis. Statistics tell us that 90% of people who get a recurrence of cancer die within 5 years. We can now see a metastasis coming much earlier than when the tumor has grown big enough to absorb enough radioactive glucose to light up on a PET scan.

Some early detection tests find substances present in the blood when cancer is present. For example, we can now test for the ENOX2 protein, which is found only on the surface of a malignant cancer cell; this protein is not found in the blood of a person without cancer. We also can test for thymidine kinase (TK) levels, which go up significantly when there is a rapid amount of cell division, a hallmark of cancer's growth. Other tests look for carcinoembryonic antigens and phosphohexose isomerase (an enzyme implicated in metastasis).

Additionally, we are moving beyond the idea that chemotherapy is a one-size-fits-all treatment. Oncology is evolving to a more personalized approach, and we can now test a blood or tissue sample against the many possible chemo drugs available to see which ones would be most effective, and not expose patients to the toxicity of those drugs which won't be effective for their particular cancer.

We can also use a blood sample to test which of more than 40 natural, biological therapies will be most effective for each person. The list ranges from artemisinin and ascorbic acid to metformin and mistletoe.

It is very common that once cancer gets a foothold, it progresses for 8 to 10 years before it is detected. New advances in technology bring us a new era, one that will change the way cancer is detected. The great news for patients is that this kind of early detection will not focus just on treatment, but also on interventions to head off a formal diagnosis.

Jenny Hrbacek, RN, is the author of *Cancer Free! Are You Sure? A Guide to Early Detection Tests*, published in 2015. She was diagnosed with breast cancer in 2009 and was told that the surgery and chemotherapy which she undertook would make her cancer free. Jenny began to research cancer and testing and learned that she was not cancer free, and that there were many options besides waiting every 6 months for the standard tumor marker tests. She now teaches and consults with cancer patients. She can be reached at www.cancerfreeareyousure.com.

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A Doctor Debunks Assumptions About Medicine

review by Ira L. Goodman, MD, FACS, ABIHM, FAARM

Less Medicine, More Health: 7 Assumptions That Drive Too Much Medical Care, by H. Gilbert Welch, MD, MPH
Beacon Press, © 2015; hardcover; 240 pp.

Gilbert Welch is an epidemiologist from Dartmouth who has published widely on the overuse of conventional medicine. His two previous books, *Should I Be Tested for Cancer?* in 2006 and *Overdiagnosed* in 2012, were in the same genre, were well referenced, and espoused a rational argument against the predominant sentiment that early diagnosis is always preferable. His latest book is more lay friendly but offers a great deal to the physician audience. He lays out the 7 assumptions that drive too much medical care and debunks each one. These are: (1) all risks can be lowered; (2) it's always better to fix the problem; (3) sooner is always better; (4) it never hurts to get more information, (5) action is always better than inaction; (6) newer is always better; and (7) it's all about avoiding death. The current book is more about therapy as opposed to diagnosis and screening, although the threads of his philosophy and prior books (which are both excellent) are clearly evident throughout. I found his casual style and anecdotes very entertaining. He distinguishes among data, information, knowledge, and wisdom. It's easy to collect

data but hard to produce useful information, and even harder to know what to do with all of it. Too many data can cause much more harm in the form of anxiety, unnecessary follow-up testing, and coerced invasive treatments; and sometimes morbidity or mortality is the result. Our fee-for-service paradigm, aggressive "community standards," and, quite frankly, greed all can conspire against the well-being of a patient.

I loved Welch's metaphors and stories throughout the book. One involves the "barnyard" of cancer types that he calls birds, rabbits, and turtles. The birds are the aggressive cancers that fly out of the barn way before any screening or diagnosis is applied. They metastasize early, so early diagnosis is not helpful. The turtles, on the other hand, are extremely slow growing cancers that are never destined to be clinically significant anyway and when discovered can lead to mutilating treatments when the patient is frightened into action. Prostate cancer is of course the poster child for turtles. Screening for turtles does more harm than good. The rabbits are the cancers that if detected early can be controlled to the benefit of the patient. The problem, of course, is that there are many more turtles diagnosed and treated than birds or rabbits. Therefore there is an epidemic of diagnosis, screening initiatives, and treatment modalities that is completely out of control. We all know normal people who have been transformed into "survivors" who are consumed with anxiety for the rest of their lives after having been diagnosed and treated for diseases that probably would never have affected them clinically in their lives.

I found the book well written, enjoyable to read, and convincing. I highly recommend, however, reading all Welch's books in the order that they were published to benefit from all of his research and insights.

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A Plea for Change in the Approach to Cancer

review by Flora Biancalana, MD, family physician

The Good Fight: a Story of Cancer, Love and Triumph, by Greg Holmes, PhD, and Katherine Roth, MD
Paradox Press
© 2014; $16.99; 380 pp.

Family practice physician Katherine Roth, MD, and her psychologist husband Greg Holmes discovered in 2004 that Greg had a rare and fatal carcinoma of the sinuses. Greg began the expected medical path of radiation therapy and chemotherapy. However, Katherine, despite the shock of such a diagnosis, began to devote hours of research into alternative therapies directly countering continued negative and unbelieving input and comments from her medical colleagues. This book tells of their indomitable courage to value the life in Greg through using acupuncture, herbs, medicinal mushrooms, and specialized diets and by embracing the spiritual realm. They, each in their own way, explore the field of psychoneuroimmunology, the network of how the mind, emotions, and nervous system influence the immune system.

In an almost journalistic style, the book is divided between portions written by Katherine and portions written by Greg. In this manner, we discover an inordinately convincing drama of one couple's refusal to accept the negative condemnation from traditional oncology and seek out a form of "medicine" that embraces all aspects of healing. The book includes information on critical supplements (MCP, curcumin, grape seed extract, quercetin, etc.), controversies of antioxidants in conventional cancer treatment, using medicinal mushrooms, the importance of maintaining a healthy GI system, and the potential of proteolytic enzymes. This information is presented in a way that a nonmedical reader can understand, with recipes and daily administration guidelines. Despite the inclusion of technical information and references, their story is carried by a powerful narration of love and commitment written with sincerity and profound emotions.

For years there has been a divide between Western medicine as we know it and the diversity of other healing arts including Eastern medicine. The integration of these different modalities as so clearly detailed in this book makes it harder to simply discount "holistic" or "alternative" medicine. This compelling true story of a couple's struggle with the diagnosis of cancer takes us on an emotionally profound journey – one that hopefully will open doors, insights, and appreciation for all the modes of healing and therapy that most assuredly do have merit, as these bright and informed writers make clear.

Katherine and Greg's story is a plea for change in the way our medical system approaches cancer and the delivery of its treatment. This is a powerful book that belongs in the hands of everyone as we prepare for the changes that simply must come in our struggle to improve health care. This book belongs in the curriculum of every medical school and in every library in this country.

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Cannabis for Lyme Disease and Related Conditions: Scientific Basis and Anecdotal Evidence for Medicinal Use

by Shelley M. White
BioMed Publishing Group; available from www.CannabisForLyme.com
© 2015; $24.95

After struggling to heal from Lyme disease using long-term antibiotics for a year, I turned to natural medicine and began executing Stephen Buhner's Lyme Borreliosis protocol. After approximately a year on Buhner's protocol, I had greatly improved, but felt I had reached a stalemate in my healing progress and still had one last obstacle to overcome. Desperate for a solution to propel me to a symptom-free lifestyle, I decided to experiment with cannabis. Although I knew little about its medicinal properties in relation to Lyme disease at the time, I knew it had over 700 healing components and was desperate enough to heal that I did not hesitate to use myself as a human guinea pig.

The first time I used cannabis, I smoked it immediately prior to going to bed. As a result, I experienced significant cognitive improvements the next morning. Eventually, I began using cannabis oil instead, a decision which I will discuss herein under the Forms and Methods section of this book. Within a few months of using cannabis oil, alongside Stephen Buhner's core protocol for Lyme disease, I became symptom free. It is important to note that I experienced extreme Herxheimer reactions during the process, a subject I will also cover in further detail in this book.

Chemical Constituents of Cannabis

A large variety of chemical compounds have been identified in cannabis, totaling over 700 to date. While many of these compounds are found in other plant species as well, some are unique to cannabis alone, such as cannabinoids. Cannabinoids are the most well-known chemical constituents in cannabis, and they are more frequently and extensively researched than any other compound in cannabis.

The medicinal properties of cannabis stem from their ability to interact with the body's endocannabinoid system, which is located throughout the body and is composed of neuromodulatory lipids and their receptors.

Cannabinoids bind to these receptors to modulate important bodily functions such as how an individual moves, reacts, and feels, as well as to regulate physiological processes including, but not limited to, appetite, pain interpretation, memory, and mood. Over 66 cannabinoids in cannabis have been identified. Of these, delta-tetrayhydrocannabinol (THC) and cannabidiol (CBD) possess the most well known medicinal benefits.

Delta-9-tetrahydrocannabinol (THC) is responsible for the psychoactive effects of cannabis. A large majority of the medicinal benefits of cannabis are attributed to THC, including its functions as an anti-epileptic, anti-inflammatory, anti-depressant, appetite stimulant, pain reliever, antiemetic, and analgesic. It is useful for treating high blood pressure, glaucoma, cancer, and can improve cognitive functions by sharpening the mind and enhancing all sensory functions including sight, hearing, and sensitivity to colors.

Cannabidiol (CBD) is a non-psychoactive cannabinoid that has a broader spectrum of known medicinal activity than any other cannabinoid. It is used in the treatment of autoimmune disorders, epilepsy, cancer, psychosis, inflammatory conditions, depression, muscle conditions, and more. It is a potent antioxidant with the ability to prevent glutamate toxicity, prevent cellular damage, and protect the brain from ischemic damage. Due to this, CBD may prove beneficial in the treatment of Lyme disease and other neurodegenerative disorders that cause oxidative stress.

Some of the other cannabinoids with known medicinal benefits include cannabinol (CBN), cannabigerol (CBG), and cannabichromene (CBC).

Also of importance are the terpenoids and flavonoids found in cannabis. Terpenoids, which are also found in mammals where they serve as vehicles to expel parasites, tend to have a synergistic effect with cannabinoids and increase their efficiency as bactericidal agents. Terpenoids in cannabis help counteract THC-induced anxiety and lend to its effectiveness at relieving symptoms of depression, pain, brain inflammation, joint inflammation, addiction, and epilepsy. The flavonoids in cannabis are called cannaflavins. Pharmacological activities of cannaflavins are shown to be up to thirty times more effective at reducing inflammation than aspirin, making them of benefit for many Lyme patients with inflammation-related pain such as arthritis. On a biochemical level, cannaflavins act as powerful antioxidants and promote glutathione levels.

Other identified chemical constituents in cannabis include terpenes, proteins, amino acids, carbohydrates, fatty acids, non-cannabinoid phenols, ketones, essential elements, esters, aldehydes, minerals and more. My book offers more in-depth information on the properties of many of these chemical constituents.

Species and Strains

The plant genus Cannabis has three species, each with different chemical constituents and medicinal properties. Cannabis Sativa and Cannabis Indica are the two most commonly used. The third species of cannabis, C. Ruderalis, is rarely used. Accounting for the vast majority of cannabis strains are "hybrids" consisting of a combination of Indica and Sativa. The percentages of Indica and Sativa in any given hybrid strain vary greatly.

Indica dominant strains produce more physical, non-psychoactive effects than Sativa due to the fact that they have a higher ratio of CBD to THC, thus making them ideal for problems such as insomnia or pain. Sativa dominant strains, which are dominant in THC and have relatively low amounts of CBD, are more mentally stimulating and are useful for mental activities such as concentration, focus, and creativity.

Personally, I prefer to use a strain with a relatively balanced 50/50 ratio of Sativa and Indica for treating Lyme disease - such as the strain "trainwreck," which has proven to be the most useful strain for me in regards to healing from Lyme disease and Lyme disease co-infections.

Cannabis as a Bactericidal Agent

Due to the steady emergence and continued increase of drug resistant bacteria, new classes of antibacterial agents are urgently needed. As history shows, synthetic, man-made antibacterial agents lack the ability to effectively eradicate the ever-evolving bacteria in our ecosystem once they successfully deem human bodies as their hosts. Initially effective antibiotics are rendered relatively useless over time. For example, resistance to the class of antibacterials most commonly used to treat E. coli induced urinary tract infections, fluoroquinolones, exists worldwide. When first introduced in the 1980s, there was virtually no bacterial resistance to fluoroquinolones.

The diversity in the characteristics of present day bacteria, such as spirochetes, is unparalleled in nature compared to the characteristics they displayed as little as five years ago. On the contrary, the pharmaceuticals used to treat them have remained very much the same.

From 1983-1987, approximately 16 new antibacterials were approved by the FDA, while under five have been approved since 2008. Many pharmaceutical companies have ceased research and development of antibacterial drugs, lending to the sharp decline of new antibacterials released in the past 30 years.

Coincidentally, the past 30 years fall grotesquely in alignment with the time period in which spirochetes have rapidly evolved into a dangerously aggressive species of bacteria. Although plants such as cannabis are equipped with secondary metabolites that display antibacterial qualities potent enough to effectively target, reach, and treat drug resistant bacteria, plants in general still remain markedly unexploited antimicrobial agents.

Research indicates that cannabis is an excellent and effective bactericide, meaning it is able to destroy or inhibit the growth of bacteria, due to its impeccably composed chemical profile. Its compounds are able to bypass the healing powers, or lack thereof, of man-made bactericides like antibiotics in order to effectively kill drug resistant bacteria or "superbugs." Compounds in cannabis known as cannabinoids, for example, appear to go unscathed by mechanisms typically used by bacteria to evade antibiotics.

In the case of Lyme disease, bacterial die-off from cannabis is evident as well, often sparking the Jarisch-Herxheimer reaction, also informally referred to as a "Herxheimer reaction," "Herx," or "Herxing." A Herxheimer reaction is instigated when dying bacteria release their endotoxins into the bloodstream and tissues faster than the body can successfully expel them from its system, prompting an excessive inflammatory response. Simply put, toxins flood the body at a rate not proportional to the body's ability to comfortably detox them, causing an overload of toxins in the body, thus increasing inflammation and worsening symptoms.

When treating myself with cannabis oil, I initially experienced painful herxheimer reactions due to the fact that I failed to simultaneously employ proper detoxification methods. Eventually it became clear that I needed to implement various detoxification methods into my treatment. The most helpful methods I have found include hydrogen peroxide and baking soda baths, chlorella, zeolite, infrared saunas, and activated charcoal. However, everyone is different, so experimenting with various different methods under the care of a medical professional to find the best ones for each individual case is often necessary.

In regards to dosing, the ideal amount to take varies among individuals due to the fact that each case of Lyme disease is different. Factors such as the presence of different co-infections or gene mutations make it difficult to establish a broad spectrum standard for dosing. Therefore, starting at the lowest possible dose and slowly increasing the dosage to a rate tolerable per individual is advised.

To summarize, when taken with the intent of killing bacteria from infectious diseases such as Lyme disease, one should slowly increase the amount of cannabis they take in order to prevent a build-up of toxins from rapid bacterial die-off. Furthermore, just as with any other Lyme disease treatment, detoxification should not be ignored during treatment. Working closely with a physician or herbalist who is open to discussing the use of cannabis is strongly recommended.

In addition to the above information, my book covers the legalities of medicinal cannabis use, forms and methods of use, and the various symptoms and conditions related to Lyme disease that cannabis has the potential to manage. Such symptoms and conditions include arthritis, nerve pain, ADHD, depression, muscle spasticity, cachexia, nausea and vomiting, seizures, anxiety, sleep disorders, migraines, memory loss, episodic rage, stress, psychosis and schizophrenia. The book was created with the intention of helping readers develop their own individualized treatment plans, and/or determine which forms, methods, and strains of cannabis would be most beneficial for their specific case. To learn more about my book, visit www.CannabisForLyme.com.

Conclusion

Scientific evidence and anecdotal experience do not support the conclusion that cannabis is a "cure" for Lyme disease. In fact, the subject of whether or not it is possible to fully cure advanced cases of Lyme disease is still a heated debate in the medical and Lyme communities alike, due to the elusive nature of the bacteria. I do, however, feel comfortable saying that cannabis oil greatly reduced the severity of my symptom picture and improved my quality of life while going through Lyme treatment. Furthermore, the published research on cannabis is very promising and strongly supports further exploration of cannabis use for Lyme disease. Likewise, many personal stories confirm that cannabis helps Lyme patients. Some of these stories are included in the Appendix of my book.

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Shelley White is the author of *Cannabis for Lyme Disease and Related Conditions*, published by BioMed Publishing Group. Learn more at www.CannabisForLyme.com. Shelley also works as a writer and editor, and is training to be a master herbalist specializing in Lyme disease and other infectious diseases. She has served as the publisher and editor-in-chief of *Public Health Alert*, a magazine covering stories about Lyme disease and related conditions. She has written for various sources, including Natural News, Mind Body Green, Collective Evolution, and Truth Theory. The topics that she most frequently covers include cannabis, psychedelics, pharmaceuticals, infectious diseases, alternative health, and consciousness.

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Nutrients and Breast Cancer: An Excerpt and Update

by Helayne Waldman, EdD, MS
from the book *The Whole Food Guide for Breast Cancer Survivors*
by Helayne Waldman, EdD, MS, and Edward Bauman, PhD

Prescription Drugs and Nutrient Depletion

A critical matter that's often overlooked by both medical professionals and consumers alike is the profound effect that pharmaceutical drugs can have on the absorption, utilization, and/or excretion of nutrients. The chart below provides "at a glance" help in understanding these effects, showing the most common depletions from drugs whose use is widespread; note that many if not most blood pressure and prescription cardiac medications have a magnesium-depleting effect as well.

Prescription Drug Category	Nutrients Depleted
Antibiotics	
Antibiotics (general) amoxicillin, penicillin, Keflex	Friendly intestinal flora, B vitamins, vitamin K, vitamin C
Tetracycline antibiotics	Friendly intestinal flora, calcium, magnesium, iron, zinc, B6, B12
Isoniazid (tuberculosis)	Vitamin B3, B6, vitamin D
Neomycin	Beta-carotene, calcium, magnesium, iron, potassium, vitamin A, B12
Trimethropim, Bactrim, Septra	Friendly intestinal flora, biotin, folate, inositol, B vitamins, vitamin K
Anticonvulsants	
Phenobarbital and barbiturates	Vitamin D, K, calcium, folate, biotin
Phenytoin (Dilantin)	Vitamin B1, B12, biotin, folate, vitamin D, calcium, Vitamin K,
Antidepressants	
Tricyclic antidepressants: amitriptyline, Doxepin, clomipramine, Tofranil	Coenzyme Q10, vitamin B2
SSRIs: Prozac, Zoloft	Melatonin
Antidiabetic drugs	
Sulfonylureas: Micronase, Diabeta, biguanides	Coenzyme Q10, vitamin E
Glucophage	Coenzyme Q10, vitamin E, folate
Anti-inflammatory drugs	
Carbamazepine, Tegretol	Vitamin E, folate, biotin
Primidone	Folate, biotin, vitamin D, K
Valproic acid	Folate, carnitine

Drug-Induced Nutrient Depletions
Adapted with permission from Designs for Health Ltd.

Note: This is just a sample list. For a complete reference on drug-induced nutrient depletions, see *The Nutritional Cost of Prescription Drugs*, by Ross Pelton and James LaValle, or *The A-Z Guide to Drug-Herb-Vitamin Interactions*, by Dr. Alan Gaby et al.

Drug-induced nutrient depletion can lead to further health challenges, as your cells need all vital nutrients all the time. Be sure to discuss with your nutritionist or integrative physician the ways in which you can compensate for any deficiencies your medications may be causing.

We realize that the subject of supplements is very confusing for many people. Below are some common questions that we have gotten from clients over the years about supplements.

What's in a Label?

RDA stands for recommended daily allowance. Today, most multinutrients will give either an RDA or a % DV value on the label as general nutrition guidelines for consumers. The underlying concept is that these allowances should prevent deficiency diseases associated with each nutrient. For example, 75 mg of vitamin C is the amount deemed necessary to prevent scurvy. However, it is not the amount thought necessary by nutritionists for optimal health. What's more, such generalizations do not work for some segments of the population, a concept called *biochemical individuality* introduced by scientist Dr. Roger Williams. Williams was the first to describe how differences in individual anatomy, physiology, and genetics determined individual nutritional requirements.

Tip: A poorly formulated supplement will have 100% DV of each nutrient. We recommend against this type of supplement, as quality manufacturers know that some nutrients are used up more quickly than others (for example, the B vitamins) and some DVs are set at unrealistically low levels (e.g., vitamin C.) On the other hand, some nutrients may be toxic at doses above the RDA (e.g., vitamin A, iron). A high-quality manufacturer will take this all into account in creating a multinutrient formula that reflects a practical understanding of how nutrients behave in the body.

How Do I Know What Form of the Nutrient Is Best?

All nutrients come in many forms. We ask that you keep two basic principles in mind. First, you'll want a nutrient which is in a form as close to the way that nature made it as possible. The simple truth is that synthetic products are far less expensive and have a longer shelf life than natural substances. As such, they are the darlings of the low-price chain stores and many pharmacies. Look for a brand that says "food-based" or 100% whole food. That way, you are not only getting the nutrients, but the cofactors, enzymes, bioflavonoids, and other phytochemicals that help the nutrient perform its job better.

Second, we suggest you familiarize yourself with nutrients that come in "families" and understand that ingesting only one "member" of the family can be problematic. An excellent example is vitamin E. Vitamin E actually consists of a large cast of characters: first there are the tocopherols – alpha, beta, delta, and gamma. Then there are the tocotrienols – also alpha, beta, delta and gamma. Ideally, your multinutrient label will say

"mixed tocopherols" or "mixed tocopherols and tocotrienols." An isolated form of one part of a nutrient can easily throw the other parts off balance.

It's also useful to know whether the nutrient is in its active or precursor form. In other words, can your body use it just the way it is, or does it need to go through some sort of conversion process? Vitamin B6, for example, is known as pyridoxal-5'-phosphate in its active, ready-to-be-metabolized form. Only higher-quality brands will invest the resources to provide the active forms of nutrients when possible.

Finally, if you are seeking out supplements as part of your breast cancer protection plan, be sure that the form you chose matches the form used in the research studies showing benefit. For example, selenium comes in many forms, but se-methylselenocysteine (SeMSC) is the form that's shown the most promise in recent studies for cancer prevention. Avoid multinutrients which do not divulge the form of the nutrient that they are asking you to take!

How Do I Identify a High-Quality Supplement?

If you are going to take supplements it is important to make sure that what you are getting is what your body needs. Unfortunately this is not always the case; there are several issue to consider when purchasing supplements. Here are a few of the most critical.

Bioavailability. A nutrient is only as good as your ability to absorb it. So it's good to get a handle on what makes some forms more absorbable than others. As we stated earlier, the closer to real food your formula is, the more familiar it will feel to your body. That said, there are a few other basic principles. Minerals, for example, are notoriously hard for the body to absorb in both food and supplement form. It's estimated by Albion Labs in Northern California that typical absorption rates for minerals range from 10% to 45% (Bauman. Nutritional Supplements: Can't Live With them, Can't Live Without Them; 2004,). A process called *amino acid chelation* increases absorption. The chart below illustrates some common nutrient forms, and can serve as a guide as to which forms are preferable.

How many nutrients does it include? All multinutrient formulas will include the basics, but only a high-quality supplement will include trace minerals, which play a vital metabolic function. Look for a formula that includes chromium to assist with blood sugar regulation, silicon for hair and nail strength, boron for bone health, vanadium for insulin sensitivity, and so on. These trace minerals are of particular importance, since they are scarce in most conventional soils. A good-quality formula will include these and more.

USP certification. A supplement with the USP (US Pharmacopoeia) designation is of the highest quality. This indicates that the product has met the following standards: disintegration (you don't want your vitamin pills just sitting in your stomach!), strength, purity, and expiration (when the supplement will no longer meet these standards). If you like, you can also request a certificate of analysis from the supplement manufacturer to help insure quality control, and that the label reflects the actual contents. An authentic certificate will give details of the lab where tests were conducted, in addition to the lot number of the product tested. This is a good way to be sure that the product is free of heavy metals, pesticides, solvents, and other pollutants.

No "junk" ingredients. Avoid products with ingredient names that you can't pronounce or identify such as such as titanium dioxide, stannous chloride, and sodium metavanadate, common ingredients in drugstore supplements. Other substances to avoid could include: all artificial colors, artificial flavors, sugars, artificial sweeteners, and toxic fillers, as well as common allergens such as lactose, gluten, or cornstarch.

Questions for Professionals

Some supplement issues need to be discussed with a professional nutritionist or other holistic practitioner. For example, how do I know what dosage of a nutrient is best for me? Your needs will vary depending on your existing nutritional status, your biochemical makeup, and your individual risk factors for breast cancer. Your practitioner may suggest that you conduct specific tests that will indicate your need for specific nutrients. This upfront spending can bring large dividends in the long run, since you can then be much more targeted and judicious in the use of only those supplements that will provide the most benefit.

Other questions to ask your practitioner would be, how/when should the supplement be taken? How long should the supplement be taken? What interactions among nutrients do I need to watch for? What interactions might they have with the herbs or medications I take? Again, these are issues that are best worked out with a professional who is experienced in the use of nutritional supplements.

In short, you will usually get what you pay for. We think that it is far better to take fewer supplements of better quality than swallow a trunk full of "junk" supplements that could wind up doing more harm than good.

Keep in mind that supplements, no matter how useful, do not and never will have the same power as nutrient-dense, whole foods. They are meant to be used as an adjunct to a healthful diet, *never* a replacement. Be sure to work with your nutritionist or other holistic practitioner to determine which supplements and dosages are right for your particular situation.

Helayne Waldman, EdD, MS, is a holistic nutrition practitioner who specializes in helping women through all phases of the breast cancer journey. She is especially interested in survivorship and helping to transform the post-treatment period into a proactive, thriving time in a cancer patient's life. Dr. Waldman sits on the board of the Annie Appleseed Project (for complementary cancer treatment); is an adjunct professor and instructor at Hawthorn University, Piedmont Public Schools, and the Cancer Wellness Community; and speaks frequently on the topic of nutrition and breast cancer. Her book with Edward Bauman, *The Whole Food Guide for Breast Cancer Survivors* – a #1 bestseller on Amazon.com – is available at www.wholefoodguideforbreastcancer.com, as is a free chapter download.

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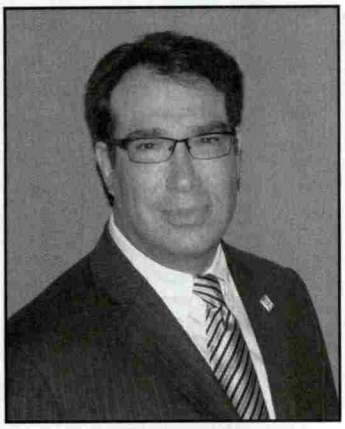
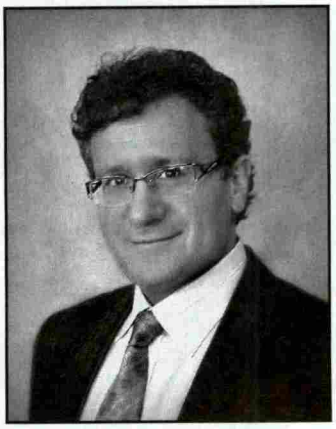
Nutrient	Look for
Vitamin A	Mixed carotenoids (fat-soluble retinoids can be used under practitioner's guidance)
B1	Thiamine HCl
B12	Methylcobalamin
Vitamin D	Cholecalciferol
Folate	Folate, Metafolin, MTHF
Vitamin E	Mixed tocopherols, mixed tocotrienols
Vitamin K	K1 and K2
Calcium	Citrate, ascorbate
Magnesium	Glycinate, taurate, citrate, aspartate
Selenium	Se-methylselenocysteine, selenomethionine
Zinc	Citrate, gluconate



Anti-Aging Medicine

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



An Anti-Aging Approach to Cancer: Harvest the Protective Potential of Foods

Eating healthfully is a cornerstone of the anti-aging lifestyle. Doing so is also a key approach for cancer protection. People who enjoy 7 or more portions of fruit and vegetables a day may reduce the risk of dying by a significant 42%. Oyinlola Oyebode and colleagues from the University College London (UK) analyzed data from 65,226 people who took part in the Health Survey for England between 2001 and 2013 to evaluate the effect of eating habits on mortality risk. After adjustment for sex, age, cigarette smoking, social class, body mass index, education, physical activity, and alcohol intake, results showed that eating 7 or more portions reduced the risk of dying from cancer by 25% and the risk of dying from heart disease by 31%. Compared to eating less than 1 portion of fruit and vegetables, the risk of death from any cause was reduced by 14% by eating 1 to 3 portions, 29% for 3 to 5 portions, 36% for 5 to 7 portions, and 42% for 7 or more. The research also showed that vegetables have significantly better health benefits than fruit. "The clear message here is that the more fruit and vegetables you eat, the less likely you are to die at any age. Vegetables have a larger effect than fruit, but fruit still makes a real difference. If you're happy to snack on carrots or other vegetables, then that is a great choice but if you fancy something sweeter, a banana or any fruit will also do you good," said Oyebode.

In this column, we share studies that suggest that each of us harvests the protective potential of foods. By enjoying a variety of colorful and flavorful foods every day, you may not only dramatically reduce your risks of cancer but also enhance the quality of your life as well.

Oyebode O, Gordon-Dseagu V, Walker A, Mindell JS. Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. *J Epidemiol Community Health*. March 31, 2014.

Citrus: Oranges, Grapefruits, Lemons

Citrus fruits are a good source of flavanols and related antioxidant compounds for which previous studies have suggested cancer risk-reductive effects. Aedín Cassidy and colleagues from the University of East Anglia (UK) followed 171,940 women, enrolled in the Nurses' Health Study and Nurses' Health Study II, to ascertain associations between intakes of total flavonoids and their subclasses, on the risk of ovarian cancer. Dietary intake was calculated from questionnaires collected every 4 years. During 16 to 22 years of follow-up, 723 cases of ovarian cancer were confirmed. Data analysis revealed that while total flavonoids were not statistically significantly associated with ovarian cancer risk, subjects in the highest quintiles of flavanol and flavanone intakes were at modestly lower risk of ovarian cancer. Specifically, dietary intakes of 75 mg/day of flavanols and flavanones were found to reduce the risk of ovarian cancer by 21%, especially in women ages 30 to 55 years. The study authors report: "Higher intakes of flavonols and flavanones ... may be associated with lower risk of ovarian cancer."

Cassidy A, Huang T, Rice MS, Rimm EB, Tworoger SS. Intake of dietary flavonoids and risk of epithelial ovarian cancer. *Am J Clin Nutr*. October 2014; ajcn.088708.

Tomatoes

Tomatoes are rich in lycopenes, antioxidant compounds for which previous studies suggest anticancer effects. Adana Llanos and colleagues from Ohio State University (US) completed a longitudinal crossover study examining the effects of both tomato-rich and soy-rich diets in a group of 70 postmenopausal women. For 10 weeks, the participants ate tomato products containing at least 25 milligrams of lycopene daily. For a separate 10-week period, the subjects consumed at least 40 grams of soy protein daily. Before each test period began, the women were instructed to abstain from eating both tomato and soy products for 2 weeks. Researchers observed that in the tomato-rich segment of the diet, participants' levels of adiponectin – a hormone involved in regulating blood sugar and fat levels – climbed 9%. This effect was slightly stronger in women who had a lower body mass index. The study authors conclude: "Increasing dietary consumption of tomato-based foods may beneficially increase serum adiponectin concentrations among postmenopausal women at increased breast cancer risk, especially those who are not obese."

A tomato-rich diet may markedly lower a man's risk of developing prostate cancer. Vanessa Er and colleagues from

the University of Bristol (UK) assessed the diets and lifestyle of 1806 men, ages 50 to 69 years, with prostate cancer, enrolled in the Prostate Testing for Cancer and Treatment (ProtecT) study. Comparing the data with 12,005 cancer-free men, the team established a prostate cancer "dietary index" which consists of dietary components – selenium, calcium, and foods rich in lycopene – that have been linked to prostate cancer. Men who had optimal intake of these three dietary components had a lower risk of prostate cancer. Specifically, tomatoes and tomato-based foods were shown to be most beneficial, lending an 18% reduction in risk in men who consumed over 10 portions a week. Observing, "Adherence to the prostate cancer-specific dietary recommendations was associated with decreased risk of prostate cancer," the study authors write: "High intake of plant foods and tomato products in particular may help protect against prostate cancer."

Llanos AA, Peng J, Pennell ML, et al. Effects of tomato and soy on serum adipokine concentrations in postmenopausal women at increased breast cancer risk: a cross-over dietary intervention trial. *J Clin Endocrinol Metab*. 18 Dec. 2013.

Er V, Lane JA, Martin RM, et al. Adherence to dietary and lifestyle recommendations and prostate cancer risk in the Prostate Testing for Cancer and Treatment (ProtecT) trial. *Cancer Epidemiol Biomarkers Prev*. 2014 Jul 13. pii:cebp.0322.2014.

Garlic

A number of previous studies report a protective effect of garlic, in both in vitro and in vivo experimental studies of cancer. Zi-Yi Jin and colleagues from the Jiangsu Provincial Center for Disease Control and Prevention (China) interviewed 1424 lung cancer patients, as well as 4543 healthy control subjects, to ascertain lifestyle behaviors (particularly, if they smoked) and dietary habits (particularly, how much garlic they ate). The data revealed that consuming raw garlic may reduce lung cancer risk by as much as 44%. Among smokers, eating raw garlic 2 to 3 times a week may reduce lung cancer risk by as much as 30%. Noting a "protective association between intake of raw garlic and lung cancer," the study authors conclude: "Garlic may potentially serve as a chemopreventive agent for lung cancer."

Jin Z-Y, Wu M, Han R-Q, et al. Raw garlic consumption as a protective factor for lung cancer, a population-based case–control study in a Chinese population. *Cancer Prev Res*. July 2013;6:711–718.

Curcumin

Known best as the substance in turmeric that gives the spice its characteristic yellow color, curcumin has been found by previous studies to exert antioxidant, anti-inflammation, anticancer, and lipid-lowering effects. Gautam Sethi and colleagues from Curtin University (Australia) completed a review of past clinical trials involving curcumin for cancer. Observing that the compound confers potent anti-inflammatory effects, the team reports that curcumin is especially effective for multiple myeloma patients and those suffering from pancreatic cancer. Noting that doses up to 12 grams appear to be nontoxic, the investigators point out that curcumin targets the key oncogenic proteins – namely, NF-kappaB, STAT3, and AP-1. The study authors write: "Anti-cancer effects are predominantly mediated through [curcumin's] negative regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other oncogenic molecules. It also abrogates proliferation of cancer cells by arresting them at different phases of the cell cycle and/or by inducing their apoptosis."

Shanmugam MK, Rane G, Kanchi MM, et al. The multifaceted role of curcumin in cancer prevention and treatment. *Molecules*. 2015 Feb 5;20(2):2728–2769.

Peppermint and Chamomile Teas

Drinking peppermint or chamomile tea, even as little as once a week, may reduce a person's risk of distal colon cancer. Lin Fritschi and colleagues from Curtin University (Australia) analyzed data from 854 incident cases and 948 controls in a case-control study of colorectal cancer in Western Australia. The researchers used multivariable logistic regression to analyze the associations of black tea (with and without milk), green tea, herbal tea, hot coffee, iced coffee, and milk with colorectal cancer. Consumption of black tea (with or without milk), green tea, decaffeinated coffee, and milk were not significantly associated with colorectal cancer risk. Those who drank herbal tea, even as little as once a week, reduced their risk of distal colon cancer.

Green CJ, de Dauwe P, Boyle T, Tabatabaei SM, Fritschi L, Heyworth JS. Tea, coffee, and milk consumption and colorectal cancer risk. *J Epidemiol*. 2014;24(2):146–153.

Anti-Aging Medicine

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Cancer May Increase Other Risks

To add to the long list of reasons to reduce cancer risk, it is important to be aware that cancer may raise a person's risk of other diseases. Flinders University (Australia) researchers report that people with cancer may be at a higher risk of developing chronic conditions such as heart disease, diabetes, high blood pressure, and cholesterol in cancer survivors, with the correlation more so elevated among men. Bogda Koczwara and colleagues analyzed data collected on the general health of 2160 South Australian adult cancer survivors with 4100 matched adults without cancer. Their team revealed a much higher prevalence of chronic conditions in the cancer group than the noncancer group, irrespective of lifestyle factors such as nutrition, physical activity, and obesity. Observing, "Despite similar lifestyle habits and BMI, the prevalence of chronic conditions was significantly higher among people with a history of cancer than among controls without cancer," the study authors submit: "This supports the importance of chronic disease management as part of health care after a diagnosis of cancer."

Berry NM, Miller MD, Woodman RJ, et al. Differences in chronic conditions and lifestyle behaviour between people with a history of cancer and matched controls. *Med J Aust.* 2014;201(2):96–100.

To stay updated on the latest breakthroughs in natural approaches that may reduce your risks of cancer, 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.

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Calendar

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Please submit an announcement of your event 90 days in advance. Event publication must be limited to 25 words or less. Multiple event listings require paid advertising. Contact calendar@townsendletter.com for details.

AUGUST 19-22: 24th ANNUAL IAACN SCIENTIFIC SYMPOSIUM – PREVENTIVE BIOCHEMICAL INTERVENTIONS & NOVEL THERAPEUTIC OVERTURES FOR THOSE WITH CANCER in Minneapolis, Minnesota. CONTACT: www.iaacn.org/symposium/

AUGUST 21-23: INTEGRATIVE ADDICTION 2015 in Myrtle Beach, South Carolina. CONTACT: 954-540-1896; Sharon@integrativeaddiction2015.com; integrativeaddiction2015.com

AUGUST 27-30: NORTHWEST HERB SYMPOSIUM – Botanicals at the Beach @ Camp Casey Conference Center, Whidbey Island, Washington. CONTACT: 425-868-0464 or 800-468-0464; info@treefarmtapes.com

AUGUST 29-30: WILLIAM REICH'S ORIGINAL ORGONOMIC DISCOVERIES FOUNDATIONS AND SCIENCE in Ashland, Oregon. CONTACT: www.orgonelab.org/events.htm

SEPTEMBER 5-7: 43rd ANNUAL ALTERNATIVE THERAPIES CANCER CONVENTION in Los Angeles, California. Doctor Symposium on **SEPTEMBER 8**. CONTACT: www.cancercontrolsociety.com

SEPTEMBER 9: TOUR OF MEXICAN CANCER CLINICS from Universal City, California. Also, **SEPTEMBER 12.** CONTACT: www.cancercontrolsociety.com

SEPTEMBER 11-13: CURING THE INCURABLES in St. Louis, Missouri. Fibromyalgia and chronic fatigue. CONTACT: iamconf.com

SEPTEMBER 12-13: BIOTICS RESEARCH presents MASTERING THE SCIENCE OF INTEGRATIVE BLOOD CHEMISTRY ANALYSIS in Houston, Texas. Also, **SEPTEMBER 19-20** in Boston, Massachusetts. CONTACT: 800-231-5777; http://www.bioticsresearch.com/node/3579

SEPTEMBER 14-15: 15th INTERNATIONAL CONFERENCE ON AYURVEDIC MEDICINE in Paris, France. CONTACT: aapna.org/conferences/15th-conference-september-2015-paris-france

SEPTEMBER 16-19: BIO-IDENTICAL HORMONE REPLACEMENT THERAPY SYMPOSIUM in New Orleans, Louisiana. Also, **NOVEMBER 19-21** in Vancouver, British Columbia, Canada. CONTACT: 561-893-8626; www.A4M.com

SEPTEMBER 17-20: AMERICAN ACADEMY OF PAIN MANAGEMENT 26th ANNUAL CLINICAL MEETING in Washington, D.C. CONTACT: www.aapainmanage.org/annual-clinical-meeting/

SEPTEMBER 17-20: 6th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE in San Diego, California. CONTACT: integrativemedicineformentalhealthconference.com/

SEPTEMBER 18-19: THE GUT BRAIN RELATIONSHIP CONFERENCE in Fort Lauderdale, Florida. CONTACT: 651-251-9623; www.innovisionhm.com/gutbrainconference/

SEPTEMBER 18-19: INTEGRATIVE THERAPIES INSTITUTE presents CHRONIC INFECTIOUS DISEASES in Vancouver, Washington (near Portland, Oregon). CONTACT: www.itiportland.com

SEPTEMBER 18-22: FOOD AS MEDICINE – CENTER FOR MIND/BODY MEDICINE in Stockbridge, Massachusetts. CONTACT: cmbm.org/professional-trainings/food-as-medicine/

SEPTEMBER 18-29: 16th INTERNATIONAL CONFERENCE ON AYURVEDA & PSYCHIATRY in Vevay, Switzerland. CONTACT: aapna.org/conferences/16th-conference-september-18-19-2015-switzerland

SEPTEMBER 19: BIOTICS RESEARCH presents THE BRAIN-NUTRITIONAL PERSPECTIVE AND CONSIDERATIONS in New York, New York. CONTACT: http://www.bioticsresearch.com/node/3580

SEPTEMBER 19-20: NOVA SCOTIA NATUROPATHIC CONFERENCE 2015 in Halifax, Nova Scotia. Presentations: Paul Herscu ND; Amy Rothenberg ND; Michael D. Allen, DC, NMD; Dr. Lois Hare ND; Dr. John Hawrylak ND. CONTACT: nsnc.info

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

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

NOVEMBER 11-14: 56th AMERICAN COLLEGE OF NUTRITION ANNUAL CONFERENCE in Orlando, Florida. CONTACT: www.naturalhealthresearch.org/annual-conference/

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

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

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

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

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

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 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

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Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

High Impact from Fresh Fruits

People would choose foods that prevent cancer if medical science could decide on what those healthful choices are! Eating 5 to 7 fruits and vegetables a day was one of the few solid pieces of nutritional advice for cancer prevention. Yet even that has been called into question. It's as if scientists are dueling with data rather than innovating ways to help people achieve more healthful diets. This column is an appeal for the practical.

Some of my colleagues claim that they find reliable answers for their patients because they only consider the peer-reviewed published medical literature. OK, I thought. I'll conduct a survey of the peer-reviewed medical literature around nutrition. Here's my list:

- Avoid gluten, but don't leave out fiber and whole grains.
- Lower your dietary fat intake, but be sure to get enough fatty vitamins and omega-3s.
- Get vitamin D, but be careful which kind and don't get too much sun.
- Identify and stop eating the foods to which you are allergic or intolerant, but focus on your overall diet to make sure it is balanced.
- Eat less but don't skip meals.
- Avoid table salt, but other salts such as magnesium and potassium are important.
- Milk is an excellent source of calcium, but be sure to avoid caloric beverages
- Vegetarian is healthful as long as you eat enough protein and minerals such as those from lean meats.
- Cook your meat thoroughly to prevent infection, but don't overcook it, because that forms harmful chemical byproducts.
- Eggs increase cholesterol so avoid or limit them, especially hidden eggs, but eggs are a nourishing protein with fats important for the brain.
- Avoid calorie-dense foods, but nuts have minerals and protein. A handful makes an ideal lunch snack if your child's school permits them.

Such medical findings are difficult to reconcile even for health professionals. All the recommendations are confusing, and some go so far as being contradictory. Discerning nourishing choices is becoming increasingly difficult.

Unfortunately there's a new addition to the nutrition contradictions list – apple eating. In the December 17, 2013, Christmas edition of the *British Medical Journal*, researchers validated the centuries-old Welsh saying that an apple a day keeps the doctor away. In the March 30, 2015, April Fools' Day edition, *JAMA Internal Medicine* conducted an analysis arriving at the opposite conclusion about daily apple consumption.

The authors took aim at a folk expression. The whole point of such sayings is to help people make good choices, so unnecessarily calling them into question is a setback for public health. I tried to infuse humor in my Medscape posting in defense of the apple idiom:

> Dr. INGRID KOHLSTADT| Preventive Medicine
> Apr 1, 2015
> There is an important "arm" to this study which has not yet been conducted. An apple a day still keeps the doctor away if you throw hard and have good aim. Happy April 1st.

Then I sent the *JAMA* editor a letter. Again I tried humor to prod my colleagues towards a closer look at their data. The Davis study found that ethnic and racial minorities were more likely to eat apples. Yet the highly visible article did not take the opportunity to bring attention to the salient public health finding. In my letter I tried to underscore the importance of access.

> First I would like to write in the margins of the JAMA editor's laughter prescription. The study by Davis et al. did not address an important mechanism by which an "apple a day keeps the doctor away," a mechanism of potentially "high impact."[1] Specifically, an apple a day keeps the doctor away especially for those who throw hard and aim.[2] The authors may wish to modify their conclusion "Evidence does not support that [consumption of] an apple a day keeps the doctor away." Alternatively the study design could include a "throwing arm."
>
> Unfortunately injuries from fruit consumption are not limited to Newton's apple. Prevention is often possible as evidenced by the absence of coconuts in palm trees lining tropical resorts. However the absence of fruit-laden trees can lead to food insecurity. Fruit gathering was a significant cause of injuries in one database, especially among minority and lower income families not privileged to the low-hanging fruits.[3,4]
>
> Davis et al. found that apple eaters were more likely to be of a racial or ethnic minority despite the 19th-century English origin of the apple-a-day idiom. Improving safe access may further consumption of apple, pineapple, pear-apple (Asian pear), love apple (tomato), custard apple (cherimoya) and other 21st-century apples. When fresh fruits aren't available people consume processed fruits with added sugar instead.[4,5] While data about apple consumption may be inconclusive, reducing sugar consumption unquestionably reduces physician visits.

Let's stick with the folk sayings that we have and make it possible for people to use them. In my opinion, if we "take aim" at the shortage of unsweetened fruits, we are likely to have a "high impact" on cancer prevention.

Notes

1. Davis MA, Bynum JP, Sirovich BE. Association between apple consumption and physician visits: appealing the conventional wisdom that an apple a day keeps the doctor away. *JAMA Intern Med.* 2015.
2. Lawson BR, Comstock RD, Smith GA. Baseball-related injuries to children treated in hospital emergency departments in the United States, 1994-2006. *Pediatrics.* 2009;123(6):e1028–e1034.
3. Negin J et al. Barking up the wrong tree: injuries due to falls from trees in Solomon Islands. *Med J Aust.* 2014;201(11):698–700.
4. Vazquez MG. Latin American immigrant youth search for fresh papaya in the US, in NutriBeeNational Nutrition Competition. In: Kohlstadt I, ed. 2015.
5. DeChristopher LR, Uribarri J, Tucker KL. Intakes of apple juice, fruit drinks and soda are associated with prevalent asthma in US children aged 2-9 years. *Public Health Nutr.* 2015:1–8.

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Nordic Naturals 'One + One = More' Campaign Benefits Big Brothers Big Sisters

On July 1, Nordic Naturals kicked off the back-to-school season with the "One + One = More" campaign to benefit Big Brothers Big Sisters of America (BBBS), a nationwide nonprofit organization that serves children ages 6 through 18. Now through September 2015, every time a consumer purchases a bottle of Nordic Naturals children's products, the company will donate $1 to the life-changing work of BBBS, for a total contribution of up to $25,000.

"Each year, as the back-to-school season approaches, we look for an organization that shares our passion for giving each generation what they need to grow healthy and strong," said Joar Opheim, founder and CEO of Nordic Naturals. "This year, we are pleased to support Big Brothers Big Sisters and their mentoring programs that help children realize their potential and build healthy futures."

BBBS provides children facing adversity with strong, professionally supported one-to-one relationships that change their lives for the better, forever. As the nation's largest donor- and volunteer-supported mentoring network, Big Brothers Big Sisters makes meaningful, monitored matches between adult volunteers ("Bigs") and children ("Littles").

Pam Iorio, president and CEO of Big Brothers Big Sisters, commented, "At the heart of the Nordic Naturals campaign is a desire to support the health and wellness of children and teens. We are appreciative of this generous commitment to support our nation's youth."

Nordic Naturals employees will support the campaign through "Build-a-Backpack Day" with BBBS at the company's corporate headquarters in Santa Cruz County. This interactive activity for the Bigs, the Littles, and the Nordic Naturals staff will provide backpacks for the start of the school year. In addition, Nordic Naturals will host a Facebook contest in August – "Mentor 4 Change" – to help raise awareness about this important organization.

All bottle sizes of Nordic Naturals children's products qualify for the promotion, including the company's best-selling Baby's DHA, Children's DHA, and Nordic Berries. More information is available at http://www.nordicnaturals.com/en/Back_to_School/One+One=More/1182.

Founded in 1995, Nordic Naturals is celebrating 20 years of revolutionizing omega-3s – pioneering a new definition of fish oil as it relates to purity, freshness, taste, and dosage. Based in Watsonville, California, the company also offers complementary nutrients essential to health. Its portfolio, distributed to over 35 countries, includes more than 200 products in a variety of flavors and formulations for adults, children, athletes, and pets. Family owned, Nordic Naturals works passionately to see generations of healthier, happier people around the world – and it's just getting started. Further information is available at www.nordicnaturals.com.

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Combination Setria Glutathione and L-Citrulline Supplementation Proven to Increase Postexercise Benefits

A new randomized, double-blind, placebo-controlled, human clinical trial published in the *Journal of the International Society of Sports Nutrition* found, for the first time, that 1 week of daily oral supplementation with 200 mg of Setria Glutathione and 2 grams of L-citrulline enhanced nitric oxide (NO) levels.[1] Setria Glutathione led to longer-lasting levels of NO by preventing its oxidative reaction when ingested in combination with L-citrulline.[1]

The study, led by Dr. Darryn Willoughby of Baylor University, was designed to determine the effectiveness of glutathione and L-citrulline on improving exercise performance, based on markers of nitric oxide (NO) synthesis.[1] L-citrulline is known to affect NO levels as it is converted to L-arginine, which synthesizes NO when ingested. However, L-citrulline supplementation alone has shown conflicting results in reference to improving exercise performance. Previous studies have indicated that glutathione stimulates L-arginine turnover and increases nitric oxide synthase (NOS). These results suggest that it may play a role in preventing oxidative reaction and sustaining the release of NO, however; its effectiveness, particularly in combination with L-citrulline, had not been determined prior to this study.

Results from the study found that after seven days of oral supplementation, levels of nitric oxide and NOx in the L-citrulline and glutathione group showed a measured increase 30 minutes postexercise when compared with the placebo group.[1] Participants in the study included 60 healthy, resistance-trained males aged 18 to 30, with a body mass index between 18.5 and 30 kg/m^2, divided into four groups that received a placebo, Setria Glutathione (1 gram), L-citrulline (2 grams), or a combination of Setria Glutathione (200mg) and L-citrulline (2 grams) for 1 week.[1] To measure the impact of supplementation or placebo during the 7-day study period, the groups were evaluated after completing resistance exercise sessions, including 3 sets of 15 repetitions at 70% to 75% of the estimated 1-RM involving the elbow flexors.[1] Participants were assessed on their maximum muscular strength at the beginning of the study, prior to supplementation and following 3 sets of 15 repetitions of the elbow flexion exercise.[1]

"In this study, we were able to determine that combining Setria Glutathione with L-citrulline not only increased blood levels of nitrite and NOx, but sustained the increases for a longer period of time, compared to placebo," said Willoughby, who is an associate professor of health, human performance, and recreation and director of Baylor's Exercise and Biochemical Nutritional Lab. "The results of this first-of-its kind study indicate that Setria Glutathione and L-citrulline may play a role in muscle protein synthesis and muscle performance when combined with resistance exercise."

"In addition to its immune health benefits, Setria Glutathione is known to work in the body to eliminate toxic chemicals, maintain cell proteins and act as an antioxidant," said Danielle Citrolo, registered pharmacist and manager of technical services for Kyowa Hakko USA. "With its reputation as the 'master antioxidant,' due in part to its role in combating oxidative stress, it's encouraging to see the benefits of Setria Glutathione supplementation extended to slowing the release of and sustaining the body's levels of NO with L-citrulline. These results give consumers a research-backed approach to increasing the effectiveness of resistance training with regular intake of L-citrulline and Setria Glutathione oral supplements."

In the same paper, similar results were seen in phase 1 in vitro (cell culture) and phase 2 rodent studies. These results combined with the human clinical trial data shows that the combination of Setria Glutathione and L-citrulline has the same positive, long-lasting benefit of enhancing nitric oxide across a variety of subjects, as well as blood levels of NOx.

About Setria Glutathione

Setria Glutathione, manufactured by Kyowa Hakko Bio Co. Ltd., is a clinically studied form of glutathione that, when taken orally, has been shown to replenish the body's reserves, which may be depleted as a result of poor lifestyle choices, stress, or natural aging. Called the "master antioxidant," glutathione helps protect cells in the body from the damaging effects of oxidative stress and toxins. Setria Glutathione is manufactured through a patented fermentation, and is patent pending for increasing natural killer (NK) cell activity and is pure, vegetarian, and allergen-free. For more information about Setria Glutathione, visit www.setriaglutathione.com.

About L-Citrulline

L-citrulline is an amino acid that plays an important role in nitric oxide metabolism and regulation. L-citrulline is converted to L-arginine in the body, leading to sustained increases in both L-arginine and nitric oxide. An ingredient with application in the areas of heart health and sports nutrition, L-citrulline is preservative free and allergen free, and contains no artificial flavors or colors. It's nonhygroscopic and highly stable, and its mild taste makes it suitable for use in a variety of formulations. This pure, vegetarian ingredient is also self-affirmed GRAS. Manufactured in the US using a proprietary fermentation process, L-citrulline is an ultrapure amino acid that carries the Kyowa Quality logo, ensuring that the ingredient is backed by our commitment to the highest manufacturing standards.

About Kyowa Hakko USA INC.

Kyowa Hakko USA INC. is the North American sales office for Kyowa Hakko Bio Co. Ltd., an international health ingredients manufacturer and world leader in the development, manufacturing, and marketing of pharmaceuticals, nutraceuticals, and food products. Kyowa is the maker of branded ingredients including Cognizin Citicoline, Pantesin Pantethine, Setria Glutathione, as well as sustamine L-alanyl-L-glutamine. For more information, visit www.kyowa-usa.com.

Notes

1. McKinley S, Andrew T, Morita M, Willoughby D. Combined L-citrulline and glutathione supplementation increases the concentration of markers indicative of nitric oxide synthesis. *J Int Soc Sports Nutr.* 2015;12(27).

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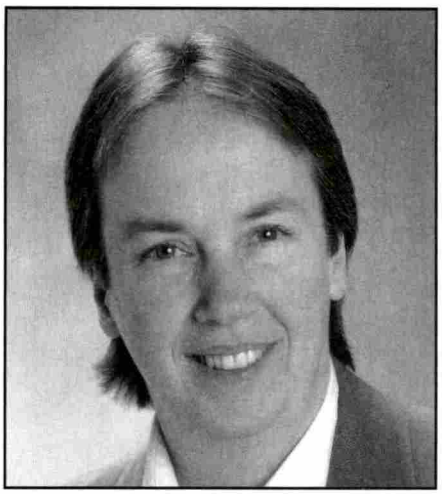

Women's Health Update

by Tori Hudson, ND and
Guest coauthor Michelle Cameron, ND
womanstime@aol.com

Cervical Dysplasia, Breast Density, Screening Mammography Controversy Continues

Vitamin D Suppositories in Vaginitis, Cervicitis, and Cervical Dysplasia

This study evaluated 200 patients with chronically recurrent infections. One hundred with chronic bacterial and/or fungal infections had no cervical dysplasia. Another 100 with chronic bacterial and/or fungal infections did have dysplasia. A total of 50 had cervical intraepithelial neoplasia (CIN) 1 and 50 had CIN 2. Of the 50 CIN 1 patients, 86% had high-risk HPV, and of the 50 CIN 2 patients, 92 % had high-risk HPV. A total of 200 women with chronic recurrent cervical infections and/or cervical dysplasia 1 or 2 were given vitamin D vaginal suppositories, 12,500 IU, 3 nights per week for 6 weeks.

The primary objectives were to evaluate the anti-inflammatory, antimicrobial, and antiviral effects of vitamin D suppositories in women with chronic recurrent cervical infections or cervical dysplasias.

1. Group 1: Cervicitis without dysplasia. Most of the women in the cervicitis without cervical dysplasia group had subjective and objective benefit. After 6 weeks, 79 of 100 women had fewer vaginal problems, less discharge, and fewer "problems after intercourse." Only 7% of patients still had bacterial and/or fungal vaginal infections after 6 weeks of therapy that required any treatment.
2. Group 2: Cervicitis with CIN 1: In women with cervicitis and CIN 1, only 10% still had a bacterial and/or fungal cervicitis. Of the 50 women, 24 were free of CIN immediately after 6 weeks of treatment, and 26 still had CIN 1. Of the 50 women, 21 still had high-risk HPV (while 43 had high-risk HPV before treatment). After a 2-year follow-up, of the 50 with cervicitis and CIN 1, the study was able to report on data from 20 of them. Of the 20 women with cervicitis and CIN 1, 3 had CIN 1 again, 1 had CIN 2–3, and one had CIN 3. The others had normal pap smears. In these 20 cases, vaginal vitamin D was ineffective.
3. Group 3: Cervicitis and CIN 2: Of the 50 women in this group, 8 still had a bacterial and/or fungal cervicitis that required treatment. Of the 50, 9 were free of CIN. Seven of these 9 were free of high-risk HPV. Twenty two women still had dysplasia and with improvement to CIN 1. Five of these 22 had negative high-risk HPV, and 19 immediately after the 6 weeks of treatment still had an unchanged CIN 2, and all still had high-risk HPV. Of the 50 in the cervicitis and CIN 2 group, 38 still had a high-risk HPV (prior to treatment with vitamin D, 46 had a high-risk HPV). After 2 years of follow-up, they had data on only 18. Of these 18, 10 cases of conization were prevented.

In this study, 100 of the 200 women had insufficient serum vitamin D values (<30 ng/ml). After treatment with vaginal vitamin D suppositories, 58 of the 100 with insufficient levels had serum vitamin D >30 ng/ml, demonstrating the likelihood of vitamin D absorption through vaginal mucosa.

Comment: This study of 200 patients with cervical infections and CIN using vitamin suppositories is only for a short period of time, but does appear to have some effect, although it is worthy of questions and doubts. The vaginal vitamin D suppositories, at 3 nights per week for 6 weeks, resulted in 79% of the women with chronic vaginal infections having fewer of the problems than when they started. It also seemed to have some important antiviral effects, especially in CIN 1, but not in CIN 2. It is difficult to assess the implications this study has for clinical practice due to the wide variety of infections (*Gardnerella vaginalis*, *Escherichia coli*, *Streptococcus*, *Staphylococcus*, *Chlamydia trachomatis*, and even *Trichomonas vaginalis*), and due to new knowledge we now have as far as the high rate of resolution of CIN I and even high-risk HPV without any treatment at all. This treatment should be avoided during pregnancy. Other than that, I see no harm in trying this treatment in CIN I and bacterial vaginosis.

Schulte-Uebbing C, Schlett S, Craiut I, Antal L, Olah H. Chronical cervical infections and dysplasia (CIN I, CIN II): Vaginal vitamin D treatment. A new effective method? *Dermatoendocrinology*. Jan 1, 2014;6:e1-1–e-1-5

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Breast Density (a Risk Factor for Breast Cancer) and N-Acetylcysteine

A small 2012 study included 25 postmenopausal women randomized to receive either 1 to 1.5 g metformin or 400 to 600 mg of NAC over a median of 10.5 months. Mammographic breast density was measured before and after completion of the study. Both groups exhibited reductions in mammographic breast density, with the metformin group eliciting reduction in 28.5% of women and the NAC group exhibiting reduction in 27.3% of cases. Altered cell proliferation, apoptosis, and DNA repair are thought to be the mechanism for the reduction in breast density. Though this is a small study and considering that pharmacological methods for mammographic bone density are few and still considered experimental, NAC supplementation may represent a promising adjunctive natural therapy to breast cancer prevention in women with dense breast tissue.

Nearly 50% of women who undergo screening mammography are classified as having either heterogeneously or extremely dense breast tissue. Dense breast tissue is defined as a greater amount of fibrous or glandular tissue than fatty tissue in the breasts. Women with dense breast tissue have a modestly elevated risk for breast cancer and the sensitivity of screening mammography is reduced. One 2007 report states a 4- to 5-fold increased likelihood of developing breast cancer in women with dense breasts versus women with low breast density. (Boyd NF et al. Mammographic breast density and the risk and detection of breast cancer. *N Engl J Med.* 2007;356[3]:227–236.)

Comment: Due to these data, and some assertive women's health scientists and activists, certain states now require that women found to have dense breast tissue on screening mammography be provided a letter informing them of these findings and then encouraged to follow up with their primary-care provider to discuss risk and screening guidelines. While this is dictated by at least 22 state jurisdictions, and more to come, most physicians have yet to urge patients to get further testing. Even the American College of Obstetrics and Gynecologists (ACOG) is currently not offering guidelines to physicians, for further testing when the mammogram detects heterogeneously dense or extremely dense tissue (grade 3 and 4 density respectively).

In a recent evidence-based review, ACOG noted that "the assessment of breast density is subjective and affected by the perspective of individual radiologists" (Committee on Gynecologic Practice. Committee Opinion No. 593: Management of women with dense breasts diagnosed by mammography. *Obstet Gynecol.* 2014 Apr;123:910).

Their statement also indicates that "use of supplemental imaging such as ultrasound, magnetic resonance imaging, tomosynthesis, or thermography has not been associated with meaningful benefits for women found at screening to have dense breast tissue." ACOG goes on to encourage clinicians to comply with applicable state laws, and support further research on the topics but as of this writing, ACOG does not recommend use of alternative tests for dense breast tissue detected on screening mammography.

Bershtein LM, Vasil'ev DA, Kovalenko IG, et al. The influence of metformin and N-acetylcysteine on mammographic density in postmenopausal women. [In Russian.] *Vopr Onkol.* 2012;58(1):45–49.

Screening Mammography Guidelines Controversy Continues

The US Preventive Services Task Force (USPSTF) issued a new and updated draft of guidelines for breast cancer screening in April 2015. These guidelines are similar to the previous one from 2009 that received widespread criticism from the American Cancer Society (ACS), the American College of Radiology, the American College of Obstetricians and Gynecologists (ACOG), and the Susan Komen Foundation. ACOG went so far as to advise patients and physicians to ignore the USPSTF. A provision was even signed into law that was meant to prevent the 2009 USPSTF

recommendation from going into effect. Once again, these updated guidelines from the task force recommends that average-risk women have screening mammograms every other year beginning at age 50 years and ending at age 74. They gave a "B" rating for mammography every 2 years for women ages 50 to 74 and "C" rating for mammography for women ages 40 to 49, which is similar to the 2009 document. They found insufficient evidence on the benefits and harms of continuing mammography in women age 75 years or older. They also state that the decision to start screening mammography before age 50 should be individualized; women who value the potential benefits of breast cancer detection more than they do the potential harms of false positives and overdiagnosis may choose to start screening at any time after age 40. The USPSTF also concludes that "some women in their 40s will benefit from mammography, while others will be harmed." Harm includes exposure to radiation from multiple tests, the stress of overdiagnosis, and unnecessary biopsies

One of the current main concerns with the USPSTF recommendations is that a "C" rating will lead to mammography no longer being covered without consumer cost-sharing for women 40-49 (about 17 million annually), and impacts coverage for women 50 and older who request and/or require annual rather than biennial screening mammograms. An additional concern from advocates for annual screening mammography starting at age 40 is that these USPSTF recommendations will cause women under 50 to delay paying attention to their breast health and may not understand that they are at low vs. higher risk ... this lack of information may not bode well for these younger women who are at risk for breast cancer (based on family history, genetics, obesity and alcohol intake) and for African-American women who are diagnosed with aggressive forms of the disease at younger ages than Caucasian women.

Some very new information in the 2015 document is related to additional imaging. Currently, 22 states have now passed laws requiring physicians to notify women whose breasts appear "dense" on mammography that other imaging tests such as ultrasound, MRI, and tomosynthesis are available, and in some cases requiring insurers to pay for these additional screening tests. Approximately half of women being screened have dense breasts and it is more difficult for a mammogram to detect suspicious lesions. These women also can have up to twice the risk of average woman of developing breast cancer. The intent of these breast density screening laws is to alert women to the limitation of mammography and encourage them to speak with their doctors about additional imaging.

The task force systematically reviewed the evidence to support adjunctive imaging for breast cancer in women with dense breasts. They found that not only was there no widely accepted standard for breast density, but that measurements changed over time: up to 1 in 5 women with "dense" breasts on one screening mammogram were reclassified into a "non-dense" category on the next examination. Although ultrasound and MRI found additional cancers, they also led to more false-positive results and biopsies. Most important, no studies examined the effect of additional screenings on breast cancer recurrence rates or deaths. The task force concluded that there was insufficient evidence to decide whether the harms of adjunctive imaging are greater than the potential benefits. The practice of recommending additional imaging beyond a mammogram, for dense breasts, is not routinely practiced by physicians, despite the fact that the patients get a letter from the radiology center reporting their dense breast status and encouraging them to speak with their physicians about additional imaging. As I mentioned in the NAC and breast density section above, ACOG does not recommend additional testing for mammographically dense breasts.

ACOG, ACS, Komen Foundation, and American College of Radiologists (ACR) urge that women decide on a screening program in consultation with their physicians – not bad advice, of course. However, I would urge all readers to see my previous column on the screening mammography controversy in 2010 and 2011, to have a deeper understanding of the benefits and risks.

I will continue to do the following with each patient:

1. Subjectively assess her risk for breast cancer; if low risk, then discuss the "four camps" for screening mammography:
   a. ACOG, ACS, Komen, ACR: yearly starting at 40
   b. USPSTF: every other year starting at 50 and until 74
   c. Several European countries: every 3 years
   d. Sweden and select others: not at all.
2. If not low risk: then discuss and likely recommend yearly starting at age 40.
3. A breast lump on exam or nipple discharge: evaluate with needed testing.
4. If moderate or severe dense breasts: discuss potential benefit of screening ultrasound.
5. Consider tomosynthesis and MRI on individual basis, in discussion with radiologists. and breast cancer surgeon.

Dr. Tori Hudson graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in many capacities over the last 28 years. She is currently a clinical professor at NCNM and Bastyr University; has been in practice for over 30 years; and is the medical director of the clinic A Woman's Time in Portland, Oregon, and director of research and development for Vitanica, a supplement company for women. She is also a nationally recognized author, speaker, educator, researcher, and clinician.

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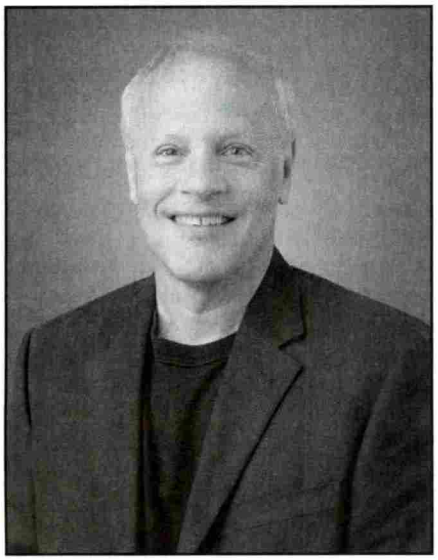

Are Some Researchers Fabricating Data?

On May 19, 2015, an "expression of concern" appeared in the *Journal of the American Medical Association* (*JAMA*) regarding a study published in that journal in 2005. In the 2005 study, conducted by a group of Japanese researchers (Sato et al.), supplementation with 5 mg per day of folic acid and 1500 μg per day of vitamin B12 for 2 years reduced the incidence of hip fractures by 78% ($p < 0.001$), compared with a placebo, in elderly patients with high plasma homocysteine levels and a history of a stroke.[1] The "expression of concern" was an announcement that various issues had been raised about the conduct, integrity, and scientific validity of the 2005 study. After communicating these concerns to Sato and evaluating his response, the editor in chief of *JAMA* contacted administrative officials at Sato's institution and requested that they conduct an investigation to evaluate the scientific integrity of the research and the validity of the reported results.[2]

I have frequently cited this study in my lectures and writings, because the results were so impressive. It is rare to find such a dramatic reduction in fracture incidence in clinical trials. I am aware of only 4 other studies in which the reduction in fracture incidence was so profound (ranging from 73% to 90%). In 3 of those studies, patients with Alzheimer's disease, Parkinson's disease, or a history of a stroke were treated with sunlight exposure.[3–5] In the other study, women with Parkinson's disease were given 45 mg per day of vitamin K2 (menaquionine-4).[6] Interestingly, all 4 of these studies were conducted by Sato et al.

My eyebrows had previously been raised by the awareness that Sato was consistently getting better results than other osteoporosis researchers. In particular, other researchers were unable to confirm a protective effect of homocysteine-lowering B-vitamin therapy against fractures in a group of patients with hyperhomocysteinemia and cerebrovascular disease.[7] However, there was no other obvious reason to question the integrity of Sato's research. Now that *JAMA* has raised concerns, I am wondering whether all of Sato's research should be considered unreliable until evidence appears to the contrary.

In the past, I have publicly questioned the validity of studies reported by two different research groups, one from India and the other from Iran. In one case, I looked more closely at certain studies because it seemed implausible that a relatively small research group could have conducted numerous large-scale randomized controlled trials in a relatively short period of time. In the other case, I looked more closely at results that seemed too good to be true, after the *Lancet* had raised concerns about scientific misconduct in relation to other research conducted by the same investigator.[8] In both instances, a closer examination of the studies revealed that some of the data were mathematically impossible or biologically inconceivable. One of the research groups that I questioned has now had 6 different studies retracted by medical journals. I am currently keeping my eye on a few other research groups whose sample sizes seem too large for their resources or whose results seem "too perfect."

How should writers and teachers deal with published research when its validity is in question? Should one just ignore it, or would it be better to present the research while voicing concerns about its reliability? And why do some researchers apparently fabricate data? The most likely reasons are that having research published may increase one's prestige in the scientific community and increase the likelihood of receiving grant money. In addition, researchers who have a financial stake in a particular product would benefit from claims that the product is beneficial.

In recent years, there has been a proliferation of open-access journals, which are supported by publication fees paid by authors. A recent study found that the peer-review process in these journals is sometimes quite lax, which means that it is easier than ever to publish questionable research. It is therefore incumbent upon us to remain vigilant in our review of research, and to maintain a healthy degree of skepticism when the situation warrants.[9]

Alan R. Gaby, MD

Notes

1. Sato Y et al. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293:1082–1088.
2. Bauchner H, Fontanarosa PB. Expression of Concern: Sato et al. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293(9):1082–1088. *JAMA*. 2015;313:1914.
3. Sato Y et al. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in hospitalized, elderly women with Alzheimer's disease: a randomized controlled trial. *J Bone Miner Res*. 2005;20:1327–1333.
4. Sato Y et al. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in Parkinson's disease. *Parkinsonism Relat Disord*. 2011;17:22–26.
5. Sato Y et al. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. *Neurology*. 2003;61:338–342.
6. Sato Y et al. Amelioration of osteoporosis by menatetrenone in elderly female Parkinson's disease patients with vitamin D deficiency. *Bone*. 2002;31:114–118.
7. Gommans J. The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial. *BMC Geriatr*. 2013;13:88.
8. Horton R. Expression of concern: Indo-Mediterranean Diet Heart Study. *Lancet*. 2005;366:354–356.
9. Bohannan J. Who's afraid of peer review? *Science*. 2013;342:60–65.

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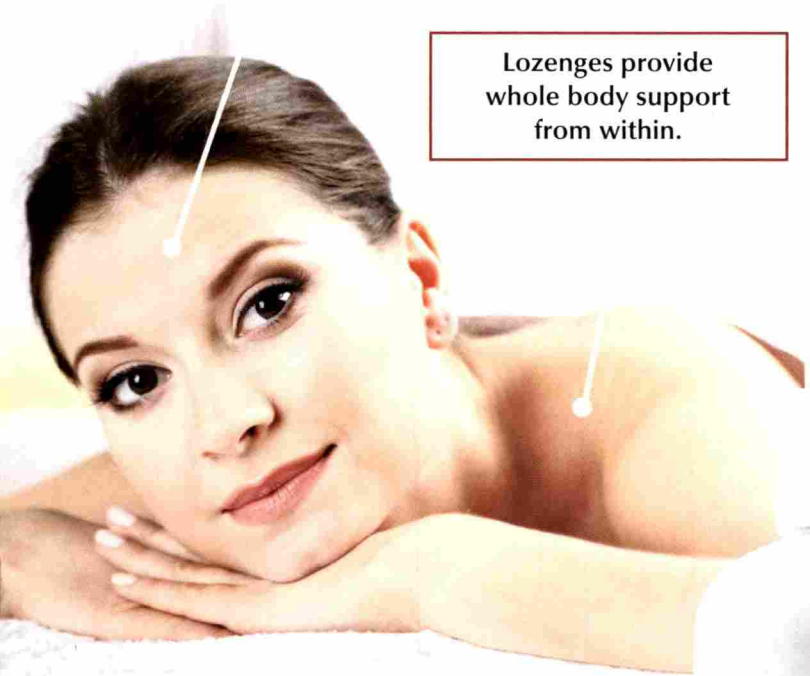

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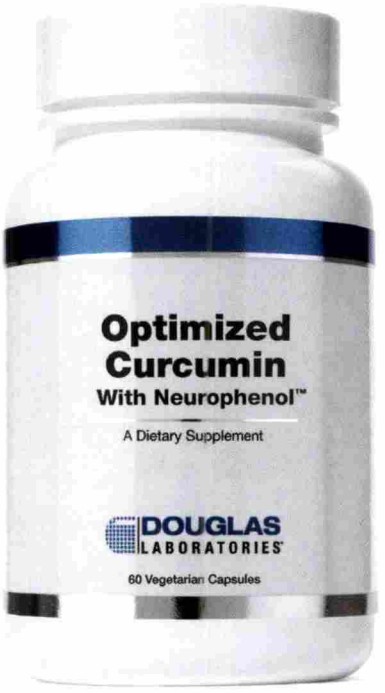

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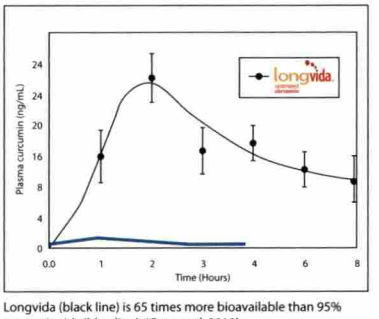
Disilvestro et al. The Ohio State University. Nutr. J. 2012 26;11:79.



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