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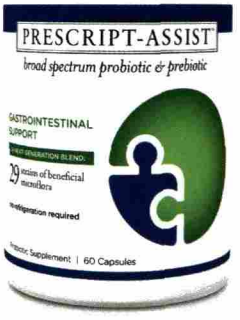

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[1] Pennisi, E. (2011). Body's Hardworking Microbes Get Some Overdue Respect. *Science, 330* (December 2010), 1619.

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From the Publisher

To Vaccinate or Not to Vaccinate

If there has ever been any issue that has separated readers of the *Townsend Letter* from public health authorities and mainstream medical scientists, it is the vaccination question. Like it or not, there is a line in the sand – those who unquestionably vaccinate versus those who question vaccination. And among those who question vaccination are those who do vaccinate only if the circumstances and options are clearly defined and overwhelmingly prudent, versus those who derail vaccination as a harbinger of future illness or adverse event and an intrusion of the government on our liberties. The antivaccination doctors and public are now being smeared as the "anti-vax" causers of the recent spate of measles and pertussis that are on the rise here in the US and abroad. Social media and the press are questioning whether the philosophical and religious exceptions for vaccination should be eliminated, that vaccinations should be compulsory. Needless to say libertarians are fuming at the notion that "immunizations" be mandated. Of course, public health has always held that parental refusal to provide "standard of care" to children with serious illness is grounds for the legal removal of the child's custody from the parents. Certainly the uptick of viral infectious disease is reason for concern, given the model for "treating the herd"; if enough individuals are unvaccinated, the risk of contagion jumps. Nevertheless, homeopathic

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Letter from the Publisher

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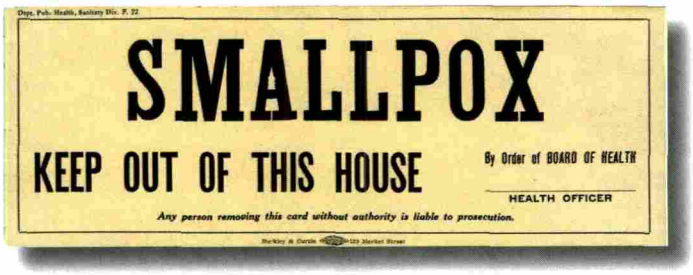
physicians despise vaccination, thinking that the vaccine imprints the system with negative "energetic factors" that potentiate risk for developing illness. Yes, science concedes that there are minimal adverse events incurred with receiving a vaccination; and for a few, very awful neurologic events do take place. That is the chance that public health is willing to take – make the majority "immunized" against disease, eliminating the scourge of childhood deaths that occurred before mandatory vaccination versus the minority who experience the unexpected and horrible. The child who incurs encephalitis is rare and tragic, and medicine dreads when this happens. That is not the same as attributing the majority of autism cases to vaccinations; the antivaccinationists who make that claim are arguing against the science. Concern about homeopathy's tenet that vaccines imprint us with the wrong energetic information and worry about an adverse event make sense, not the fear of having an autistic child. And let's stop the make-believe stories that vaccination has had no effect in curbing infectious disease. Smallpox has been eradicated, and the reason is not good hygiene, lifestyle, and improved waste-management systems – it is a long and steadfast vaccination program that started in the 19th century and continued through the 20th. There are individuals who love to rewrite history denying the truth – let's not go there with vaccinations – that the polio vaccine has eliminated polio (except now in



some Syrian refugee camps and other nonvaccinating Third World spots), and who would want to chance that their child develop polio?

So the question that we face is, "to vaccinate or not to vaccinate." The standard of care is set in stone. Without having a serious egg allergy – a serious allergy, not a positive IgG test to egg – or an immune-compromised disorder, one should receive immunizations as advised by pediatric health schedules. In the hope that there may be a chance to lessen the small risk that a horrible complication may develop with a vaccination, some parents opt to modify the schedule, lengthening the time between advised vaccinations. There may be some prudence to this – perhaps a delay between vaccinations might decrease the risk of an adverse event, although there is no science that validates this. The homeopaths do offer homeopathic medicine to counter the adverse effect of vaccination. Certainly, those children who have experienced minor adverse effects from vaccination

continued on page 8 ➤

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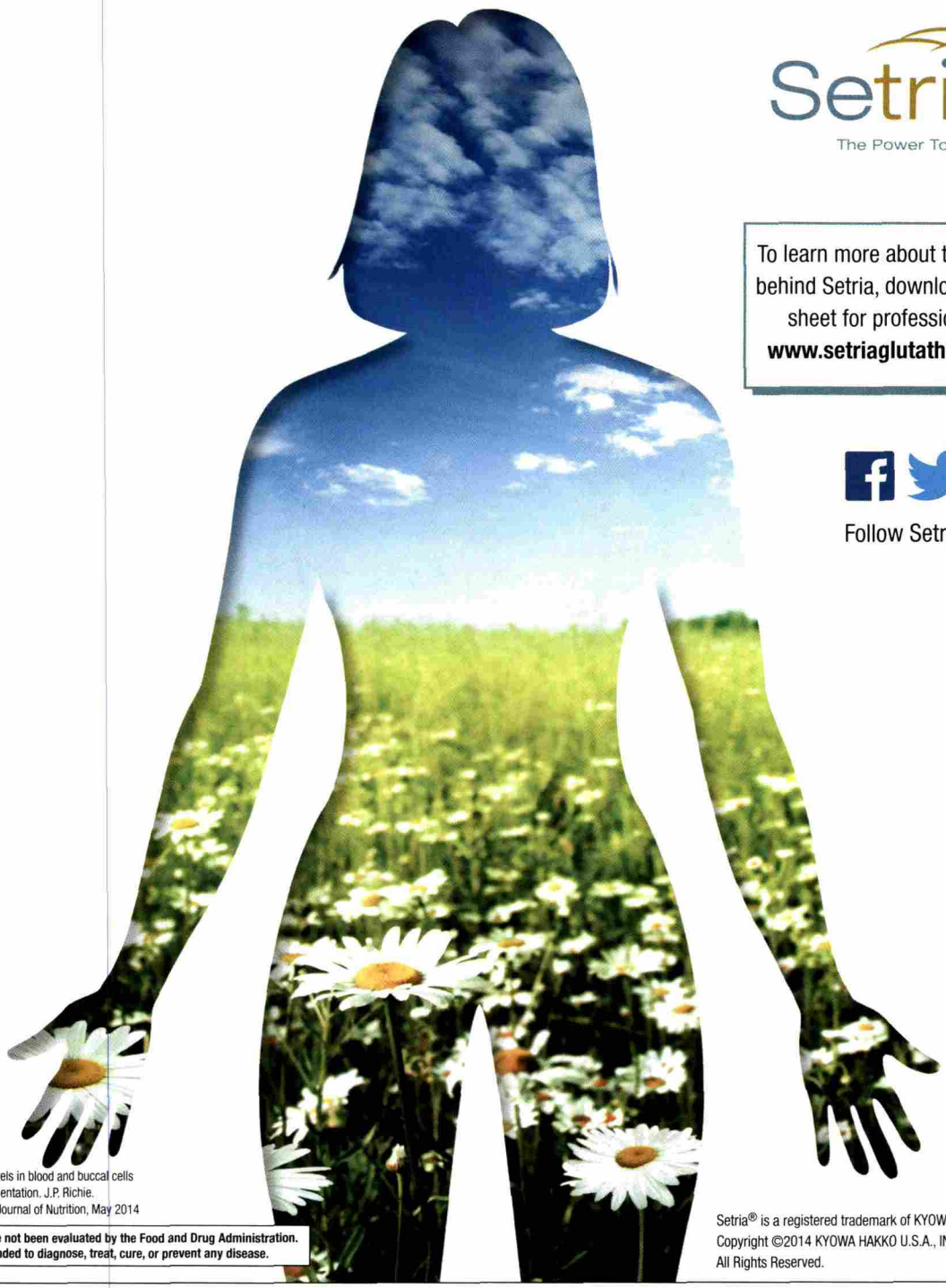

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1) Enhanced glutathione levels in blood and buccal cells by oral glutathione supplementation. J.P. Richie. Published in the European Journal of Nutrition, May 2014

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Letter from the Publisher

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deserve such treatment. But the key question is to vaccinate or not. One naturopathic physician contends that the naturopathic profession is "losing its soul" to medical standard of care and that naturopaths are abandoning their mission to foster natural care and engender immunity through individuals' experiencing the illness. Another libertarian ND argues that physicians should not forsake individual choice in deciding whether to vaccinate – there will be no end to government becoming Big Brother, ordering us to undergo diverse compulsory medical treatments. And a third ND makes the homeopathic argument that vaccines are brutal instruments that follow the allopathic model of one medicine for everyone – not individualized medicine based on understanding an individual's genomic, metabolic, and gastrointestinal microbiologic characteristics.

To vaccinate or not to vaccinate ... that is the question. As naturopathic and integrated physicians, let's not belittle the issue. Every parent needs to make a prudent choice.

Fecal Microbiota Transplantation

In our February/March 2015 issue, Mark Davis, ND, wrote about fecal microbiota transplantation (FMT). Davis is one of a growing number of physicians in the US and internationally who are transplanting stool microorganisms from healthy individuals to sick individuals. FMT has been demonstrated to be particularly effective in resistant *C. difficile* infections. Many patients who have had resistant *C. difficile* have been repeatedly treated with antibiotics, including vancomycin. The resistant infection has been so difficult to treat that FMT has been the only effective means for controlling the disease. Unfortunately, the FDA's position has been that FMT is a "drug therapy" and has not been through the rigorous evaluation required of all drugs; consequently it is not a permitted procedure without a research IND. However, physicians treating resistant *C. difficile* are permitted to transplant stool organisms without an IND.

In the December 2, 2014, issue of the *New Yorker*, Emily Eakin reports about FMT treatment in her "The Excrement Experiment" article. Ben Eiseman, MD, a surgeon in Denver, reported in 1958 about four patients treated with stool transplants in the journal *Surgery*. The patients had been given routine preoperative antibiotics and became desperately ill. When Eiseman transplanted stool obtained from maternity patients, each of the patients recovered. In Australia, a gastroenterologist, Thomas Brody, MD, read Eiseman's report and decided to use the technique on a patient who had a major GI infection after traveling to Fiji. The patient recovered and Brody implemented the procedure in his practice, treating thousands of patients.

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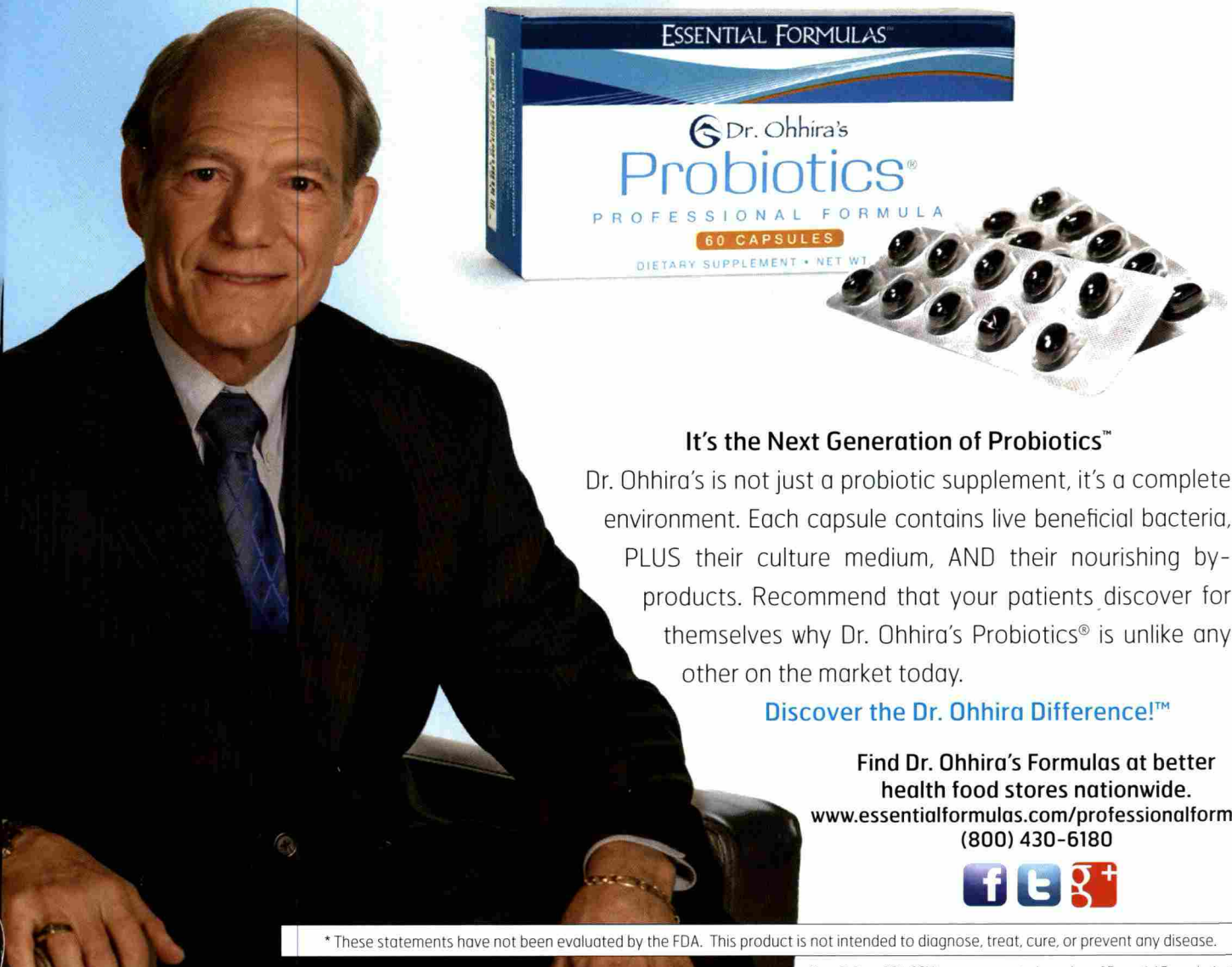

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Letter from the Publisher

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FMT has gained so much popular regard among ill individuals that many have opted to self-administer stool transplants. The Internet provides all the information needed to prepare a treatment. Eakin describes how one Crohn's disease patient requested a healthy neighbor in his apartment building to provide stool so that he could do his own home transplants.

In the meantime there has been a commercial interest in providing licensed FMT. A company called Rebiotix has designed an FMT enema that is undergoing clinical studies needed for FDA approval. Another venture, OpenBiome, developed by graduate students at MIT, is supplying clinics with "food-removed" stool slurries from screened healthy volunteers that are prepared to optimize microbiota content. OpenBiome's charge of $250 for a prepared stool transplant has not received FDA approval but the product is being used to treat resistant *C. difficile*. A research group at Massachusetts General Hospital is engineering a pill preparation of stool microbiota that appears to provide equally effective treatment as a stool transplant.

While FMT has been especially useful for treating chronic gastrointestinal illness, there is evidence that it may be useful for other inflammatory disorders. If so we may find that stool will be the centerpiece for medical treatment in the 21st century.

Triple Negative Breast Cancer

Breast cancer diagnosis and treatment are predicated on determining whether the cancer is estrogen receptor positive and/or progesterone receptor positive. Many tumors are characterized as HER2-positive. However, there are some breast cancers that are neither estrogen or progesterone receptor positive, nor are they HER2-positive. Such tumors are termed *triple-negative breast cancer* (TNBC), and they are estimated to represent 15% of invasive breast cancer in the US. Barbara MacDonald, ND, LAc, writes about TNBC in this issue of the *Townsend Letter*.

As a more aggressive form of breast cancer, TNBC has a greater prevalence in African-Americans than in Caucasians. Because TNBC is invasive, it is recommended that chemotherapy be administered early in its diagnosis. MacDonald outlines natural therapies that complement chemotherapy for managing TNBC.

MacDonald is the author of *The Breast Cancer Companion: A Complementary Care Manual: The Practitioner's Guide to Support Women Through Conventional Cancer Treatment*. A fourth edition of this book that includes an expanded review of TNBC will be published later this year. MacDonald's practice in Camden, Maine, facilitates treatment for cancer and chronic illness.

FDA Threat to Compounding Pharmacies Heats Up

Over the past year, the FDA has proceeded in determining new regulations for the operation of compounding pharmacies as well as the pharmacopoeia of what drugs and chemicals the agency will or will not permit to be compounded. As most readers recall, the outbreak of fungal meningitis caused by the injection of adulterated corticosteroids produced by a New England compounding pharmacy led to congressional approval of new FDA regulatory control of compounding pharmacies in 2013. While the FDA initially was open to advisement about the scope of these regulations, its current activity has been closed to scrutiny by the industry, physicians, and other interested parties. Among the major changes that the FDA is proposing is the division of compounding pharmacies into two separate entities, the compounding pharmacy limited to what may be compounded, and the large outsourcing facility that will manufacture drugs under strict FDA manufacturing guidelines. The compounding pharmacy will be limited to compound only 5% of its prescriptions to out-of-state patients. Perhaps the greatest change that the FDA is requiring is that compounded prescriptions may no longer be provided for general "office use." Hence a physician providing a treatment that requires a compounded prescription, such as an injectable vitamin or mineral, would be obligated to arrange for individually prescribed injections for each patient.

The potential that the FDA regulations will upend compounding pharmacies and physician practices is immense. Allison Murphy, legislative director of the Alliance for Natural Health, examines these implications in this issue.

Jonathan Collin, MD

Retraction:

Wyatt DA. Bovine Colostrum and Immune Modulation: Managing Viral Threats with PRPs. *Townsend Lett.* January 2015;378.

Use of Colostrum and Colostrum-Derived Derived PRPs in Medical Practice

We have just finished a review of our first 12 months' pediatric experience with PRP spay (Viralox®). …

~David M. Markowitz, MD, Pediatrician

Dr. Markowitz did not use Viralox in the research discussed by Wyatt. Markowitz has not used Viralox products. Markowitz did not authorize his research findings to be used by Wyatt.

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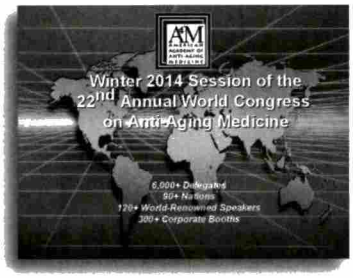

Postcard from A4M Winter 2014 Congress

The Winter 2014 Session of the 22nd Annual World Congress on Anti-Aging Medicine drew 6000-plus physicians, health practitioners, scientists, and corporate leaders to a three-day educational program that shared the latest scientific data on advanced preventive medical diagnostics and therapeutics, and emerging biomedical technologies.

Cosponsored by the American Academy of Anti-Aging Medicine (A4M; www.worldhealth.net, www.a4m.com), the world's largest leading professional medical society dedicated to educating physicians, scientists, and members of the public on biomedical sciences, breaking technologies, and anti-aging issues, the Winter 2014 Session of the 22nd Annual World Congress was the largest event of its kind in the arena of advanced preventative medicine.

The Annual World Congress on Anti-Aging Medicine is recognized around the world for the high caliber of speakers, delegates, and international government officials in attendance. Over 120 speakers, many of whom are world renowned in their area of specialization, spoke on a broad array of topics in aging intervention. Many of the subjects showcased innovations with vast potential to reshape advanced preventative medicine in this next decade.

Explains Ronald Klatz, MD, DO, A4M president: "Since its founding in 1992, the American Academy of Anti-Aging Medicine (A4M) has been one of the fastest-growing medical societies in the world, starting with just 12 doctors to become an international, member-based professional scientific medical society of 22,000-plus physicians, health practitioners, and scientists. The 6000-plus delegates representing 90 nations at this Winter Congress reaffirm the A4M's leadership role in the field of anti-aging/regenerative medicine, and underscore the undeniable inertia of the movement as well."

Adds Robert Goldman, MD, PhD, DO, FAASP, A4M chairman: "Now in its third decade of educational service, the A4M has been a major force in advancing the medical specialty worldwide, responsible for positioning the anti-aging clinical medical specialty as a leading innovative paradigm for health care in the aging nations around the world. The A4M's cosponsored educational programs in anti-aging/regenerative medicine have an expansive and impactful global reach."

◆

Vitamin E Intake Critical During 'the First 1000 Days'

by David Stauth

Amid conflicting reports about the need for vitamin E and how much is enough, a new analysis suggests that adequate levels of this essential micronutrient are especially critical for the very young, the elderly, and women who are or may become pregnant.

A lifelong proper intake of vitamin E is also important, researchers said, but often complicated by the fact that this nutrient is one of the most difficult to obtain through diet alone. Only a tiny fraction of Americans consume enough dietary vitamin E to meet the estimated average requirement.

Meanwhile, some critics have raised unnecessary alarms about excessive vitamin E intake, while in fact the diet of most people is insufficient, said Maret Traber, a professor in the College of Public Health and Human Sciences at Oregon State University, principal investigator with the Linus Pauling Institute, and national expert on vitamin E.

"Many people believe that vitamin E deficiency never happens," Traber said. "That isn't true. It happens with an alarming frequency both in the United States and around the world. But some of the results of inadequate intake are less obvious, such as its impact on the nervous system and brain development, or general resistance to infection."

Some of the best dietary sources of vitamin E – nuts, seeds, spinach, wheat germ, and sunflower oil – don't generally make the highlight list of an average American diet. One study found that people who are highly motivated to eat a proper diet consume almost enough vitamin E, but broader surveys show that 90% of men and 96% of women don't consume the amount currently recommended, 15 milligrams per day for adults.

In a review of multiple studies, published in *Advances in Nutrition*, Traber outlined some of the recent findings about vitamin E. Among the most important are the significance of vitamin E during fetal development and in the first years of life, the correlation between adequate intake and dementia later in life, and the difficulty of evaluating vitamin E adequacy through measurement of blood levels alone.

Findings include:

- Inadequate vitamin E is associated with increased infection, anemia, stunting of growth, and poor outcomes during pregnancy for both the infant and mother.
- Overt deficiency, especially in children, can cause neurological disorders, muscle deterioration, and even cardiomyopathy.
- Studies with experimental animals indicate that vitamin E is critically important to the early development of the nervous system in embryos, in part because it protects the function of omega-3 fatty acids, especially DHA, which is important for brain health. The most sensitive organs include the head, eye, and brain.
- One study showed that higher vitamin E concentrations at birth were associated with improved cognitive function in 2-year-old children.
- Findings about diseases that are increasing in the developed world, such as nonalcoholic fatty liver disease and diabetes, suggest that obesity does not necessarily reflect adequate micronutrient intake.
- Measures of circulating vitamin E levels in the blood often rise with age as lipid levels also increase, but do not prove an adequate delivery of vitamin E to tissues and organs.
- Vitamin E supplements do not seem to prevent Alzheimer's disease occurrence but have shown benefit in slowing its progression.
- A report in elderly humans showed that a lifelong dietary pattern that resulted in higher levels of vitamins B,C, D, and E was associated with a larger brain size and higher cognitive function.
- Vitamin E protects critical fatty acids such as DHA throughout life, and one study showed that people in the top quartile of DHA concentrations had a 47% reduction in the risk of developing all-cause dementia.

"It's important all of your life, but the most compelling evidence about vitamin E is about a 1000-day window that begins at conception," Traber said. "Vitamin E is critical to neurologic and brain development that can only happen during that period. It's not something you can make up for later."

Traber said she recommends a supplement for all people with at least the estimated average requirement of vitamin E, but it's particularly important for all children through about age 2; women who are pregnant, nursing, or may become pregnant; and the elderly.

This research was supported in part by the National Institutes of Health.

◆

No Deaths from Vitamins, Absolutely None: 31 Years of Supplement Safety Once Again Confirmed by America's Largest Database

by Andrew W. Saul
Editor, Orthomolecular Medicine News Service

There were no deaths whatsoever from vitamins in the year 2013. The 31st annual report from the American Association of Poison Control Centers shows zero deaths from multiple vitamins. And there were no deaths whatsoever from vitamin A, niacin, vitamin B6, any other B vitamin, vitamin C, vitamin D, vitamin E, or any vitamin at all.

Zero deaths from vitamins. Want to bet this will never be on the evening news?

Well over half of the US population takes daily nutritional supplements. If each of those people took only one single tablet daily, that makes about 170,000,000 individual doses per day, for a total of well over 60 billion doses annually. Since many people take far more than just one single vitamin tablet, actual consumption is considerably higher, and the safety of vitamin supplements is all the more remarkable.

Abram Hoffer, MD, PhD, repeatedly said: "No one dies from vitamins." He was right when he said it and he is still right today. The Orthomolecular Medicine News Service invites submission of specific scientific evidence conclusively demonstrating death caused by a vitamin.

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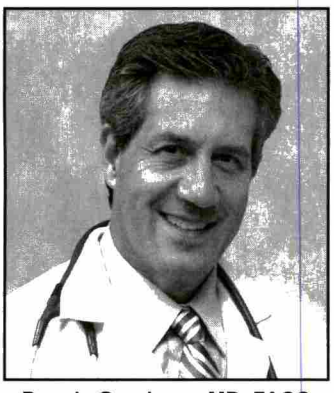
Renowned Cardiologist Dr. Dennis Goodman Joins Albion Laboratories' Scientific Advisory Board



Dennis Goodman, MD, FACC

Albion Human Nutrition, premier manufacturer of mineral amino acid chelates, today announced Dennis Goodman, MD, FACC, as the most recent addition to its distinguished scientific advisory board. Goodman joins the board in its continued efforts to provide health-care professionals, dietary-supplement manufacturers, and consumers with the latest research and clinical evidence supporting the use of minerals to enhance human health.

Goodman is the clinical associate professor of medicine and director of the Integrative Medicine & Wellness program at New York University in New York. He received his medical degree from the University of Cape Town School of Medicine in South Africa and completed his residency in internal medicine at the University of Pittsburgh and his fellowship in cardiology at Baylor College of Medicine in Houston. He is board certified in cardiology, internal medicine, integrative (holistic) medicine, and four other cardiology subspecialties. He served as the chairman of cardiology at Scripps Memorial Hospital and has been in practice for over 25 years.

"Dr. Goodman's pedigreed training and extensive clinical experience as an interventional cardiologist has given him a unique insight into the need for preventative medical practice which led him to becoming an expert in the role of magnesium in supporting health and vitality," said Jonathan Bortz, MD, chairman of the Albion scientific advisory board. "His strong academic background combined with his outspoken and passionate belief in and understanding of integrative health care makes Dr. Goodman an ideal and exciting addition to the Albion board."

Goodman has received numerous awards and recognition, was recently named one of "America's Top Doctors" by Castle Connolly, and is a sought-after international speaker who has appeared on numerous television and radio programs. Dr. Goodman has published many peer-reviewed articles and is the author of *Magnificent Magnesium, Your Essential Key to a Healthy Heart and More*, an acclaimed and informative guide on the clinical relevance of magnesium.

"I'm pleased to join the Albion Scientific Advisory Board and take part in an organization so committed to advancing mineral science and innovation," said Goodman. "I look forward to participating in the effort to bring the latest evidence-based research on mineral supplementation to the forefront for health-care practitioners and consumers alike."

About Albion Human Nutrition

Albion Human Nutrition is the premier manufacturer of "Six Stage Chelates" – patented organic mineral amino acid chelates used in human nutrition products worldwide. Building a better mineral since 1956, Albion has applied its extensive library of research to offer a more effective, bioavailable, and easily tolerated mineral for its solution providers. For more information, visit www.albionminerals.com. ◆

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Bilateral Mastectomy

An increasing number of women with cancer in one breast are choosing to have both breasts surgically removed. Bilateral mastectomy has been associated with reduced cancer incidence in women with BRCA1, BRCA2, or other high-risk gene mutations. For most women, however, bilateral mastectomy has no survival advantage over lumpectomy (removal of the cancerous tissue) and radiation therapy, according to a 2014 California study. The data for the study came from California's Cancer Registry. The registry includes demographic information, type and stage of cancer, treatment, and outcome for virtually all cancer cases in that state.

The researchers sought to determine the comparative effectiveness of bilateral mastectomy, unilateral mastectomy (removal of affected breast), and lumpectomy plus radiation. They analyzed data from 189,734 women, diagnosed with stage 0–III cancer in one breast between 1998 and 2011. Median follow-up was 89.1 months. Fifty-five percent of the women underwent a lumpectomy to remove cancerous tissue and follow-up radiation therapy. The entire affected breast was removed in 38.8%, and both breasts were removed in 6.2%. The 10-year all-cause mortality rate for lumpectomy-radiation treatment was 16.8% (95% CI, 16.6%–17.1%) compared with 20.1% for unilateral mastectomy (95% CI, 19.9%–20.4%) and 18.8% for bilateral mastectomy (95% CI, 18.6%–19.0%). The higher mortality rate in the unilateral mastectomy group may be partially due to other health problems and more limited access to care, say the authors; most women in the group had lower socioeconomic status and identified as a racial/ethnic minority.

In contrast, the bilateral mastectomy group consisted primarily of non-Hispanic white women less than 40 years old with private insurance. The use of bilateral mastectomy in this age group increased from 3.6% in 1998 to 33% in 2011. Fears about cancer appearing in the second breast may be one reason for removing an unaffected breast. Cosmetic concerns are another. "Some newer breast-reconstruction methods achieve better symmetry when both breasts are reconstructed simultaneously," according to the researchers.

Although bilateral mastectomy does not provide a survival advantage in the general population, it appears to increase survival in those with inherited mutations in BRCA1 and BRCA2 breast cancer susceptibility genes. Such mutations occur in less than 1% of the general population. About 5% to 10% of all female breast cancers occur in women with these mutations, according to *California Cancer Facts & Figures 2014* (www.ccrcal.org/pdf/Reports/ACS_2014.pdf).

A 2013 Dutch study following women with BRCA1/2 mutations (but no actual cancer) found that women who chose prophylactic bilateral mastectomy (n = 212) had a 99% 10-year overall survival rate compared with 96% for the surveillance group (n = 358). Six women in the surveillance group died (4 from breast cancer), compared with 1 in the mastectomy group. Although that woman was never diagnosed with breast cancer, she developed metastases in axillary lymph nodes, bone, and liver 3.5 years after her bilateral mastectomy. No breast cancer appeared during 1379 person-years of observation in the mastectomy group compared with 57 cases during 2037 person-years of observation in the surveillance group. The researchers conclude, "In healthy BRCA1/2 mutation carriers, [prophylactic bilateral mastectomy] when compared with surveillance reduces [breast cancer] risk substantially, while longer follow-up is warranted to confirm survival benefits."

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continued on page 23 ➤

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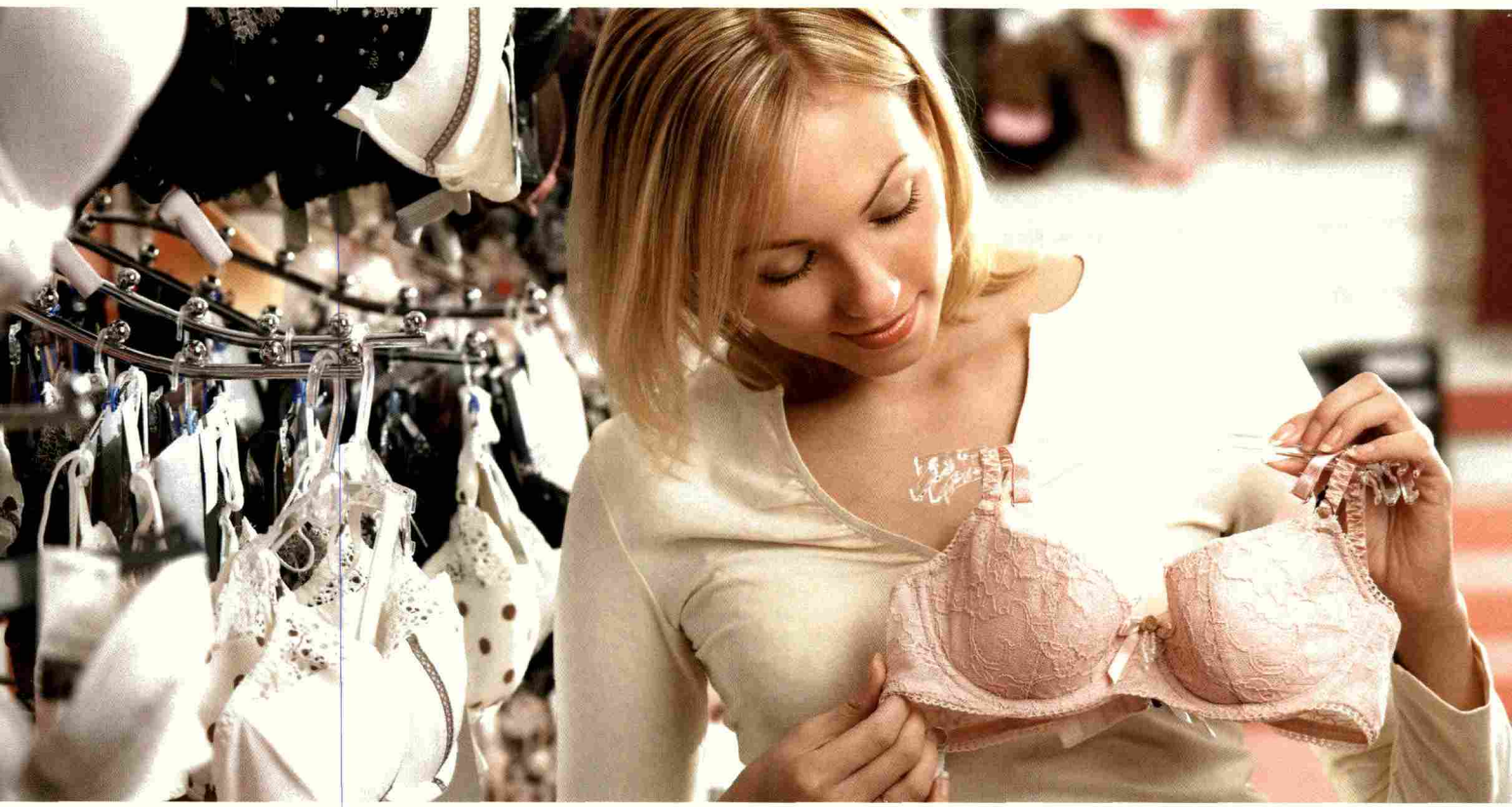

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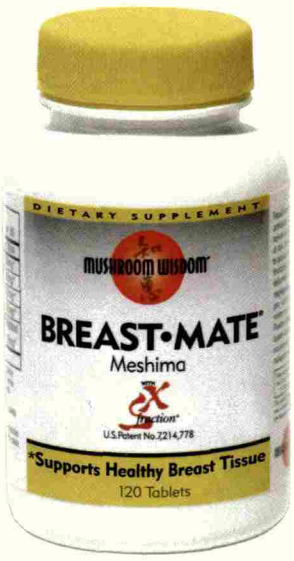

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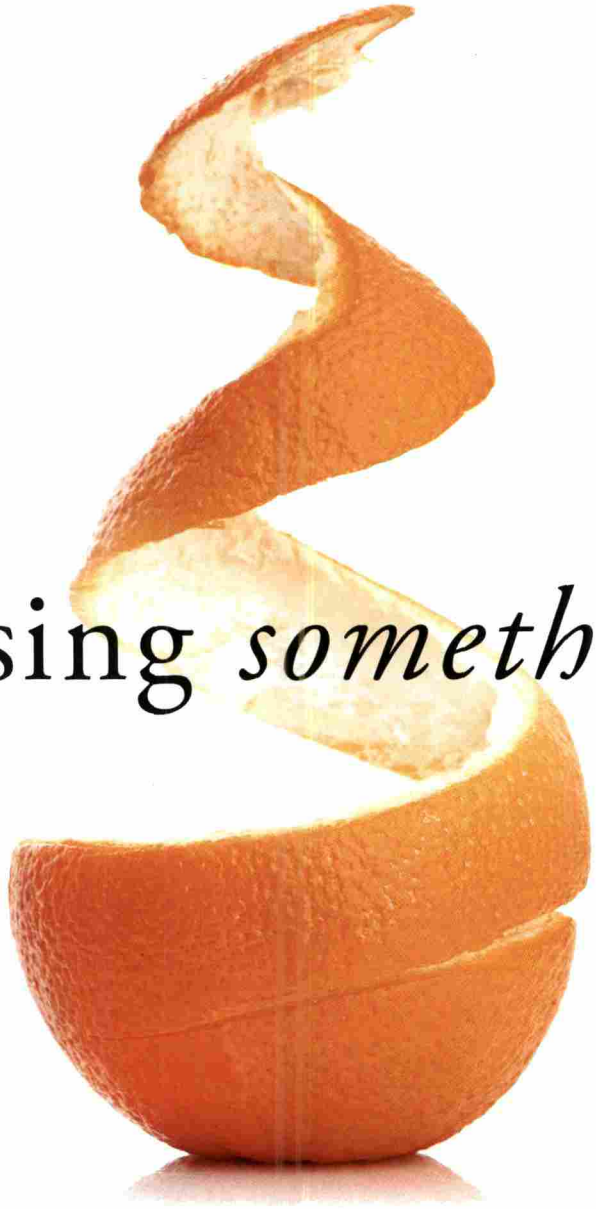

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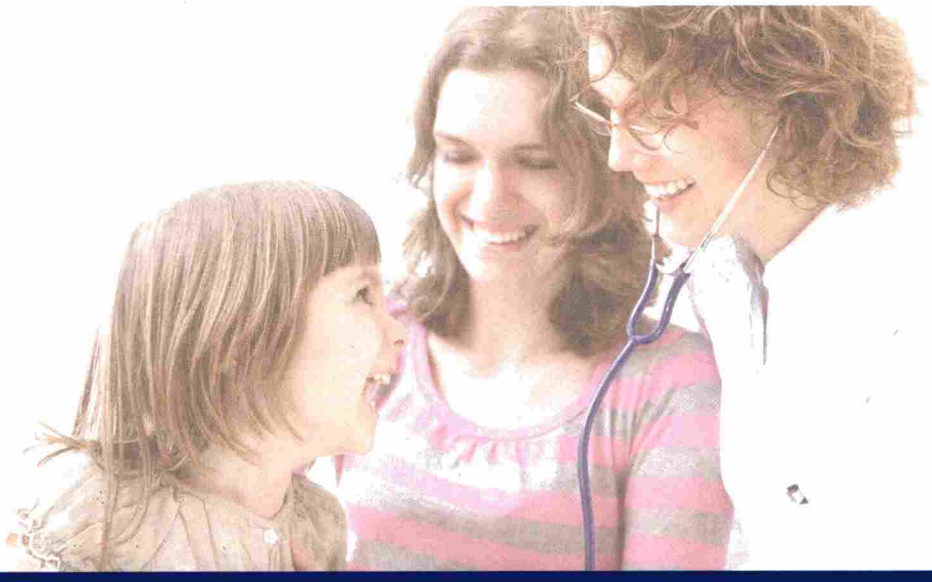

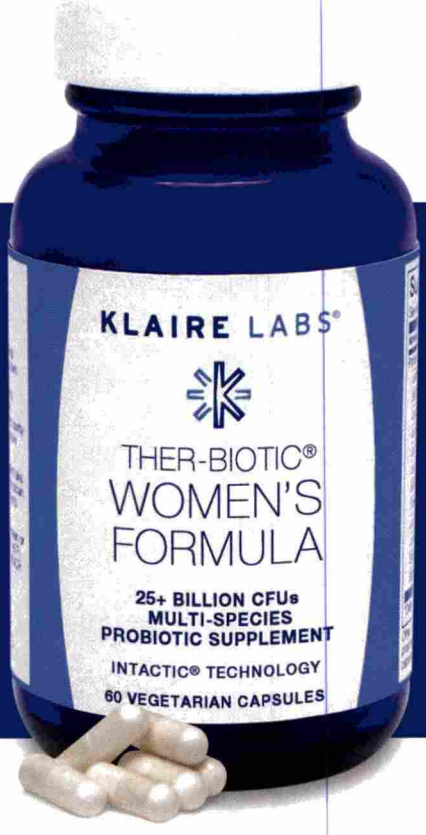

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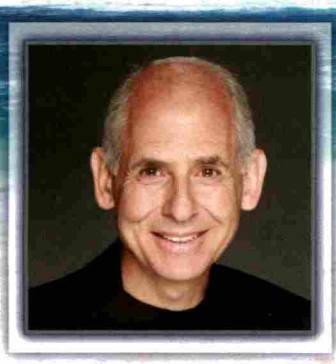

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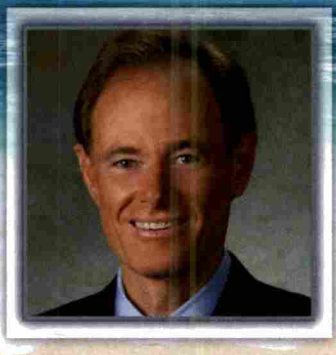

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Counting Calories

Restricting food calories to lose weight ignores an important factor: metabolic effects produced by different macronutrients. In their 2014 commentary for *Public Health Nutrition,* Sean C. Lucan and James J. DiNicolantonio write, "The statement that 'a calorie is a calorie' ... implies that any two different foods, which have equivalent amounts of potential energy, will produce identical biological effects with regard to body weight/body fatness when consumed." In reality, the body reacts to proteins, fats, carbohydrates, and alcohol differently. Food composition affects physiological responses that govern satiety, food consumption, and body composition, including production of hormones that stimulate or suppress appetite and raise or lower blood sugar.

Calorie-focused advice discourages consumption of high-fat, nutritious foods such as nuts, nut butters, avocados, olives, olive oil, whole dairy, and oily fish. Dietary fat contains about 9 kcal/gram. Protein and carbohydrates each contain about 4 kcal/gram, and alcohol has about 7 kcal/gram. The bias against fat in our calorie-focused society has led to an obsession with low- and nonfat versions of whole foods. In addition, many products marketed as "low-fat" contain higher amounts of refined, easily absorbed carbohydrates. Overconsumption of white rice, refined flour, fruit juices, and other such carbohydrates play havoc with insulin levels, produce food cravings, and may contribute to leptin resistance – producing metabolic abnormalities and increasing hunger. "The problem with trying to 'eat less' and 'move more' to achieve – and more importantly, maintain – caloric deficit or negative energy balance is that it is practically and biologically implausible," say the authors. Fatigue and hunger result, leading to compensatory eating and rebound weight gain.

Lucan and DiNicolantonio are concerned that recent proposals to highlight calories on packaged-food labels and to include calorie tables on restaurant menus simply encourage calorie-counting at the expense of food quality. Low-fat baked potato chips have fewer calories than nuts, but chips and other simple carbohydrates contribute to abdominal fat and metabolic dysfunction. In contrast, eating nuts does not promote metabolic dysfunction. Moreover, recent studies indicate that higher-fat diets that attend to food quality (such as the Mediterranean diet) produce and sustain weight loss comparable to calorie-restricted or higher-carbohydrate diets.

Lucan and DiNicolantonio advocate for whole and minimally processed foods that don't skew metabolism and encourage overeating: "As a guiding principle, the public health community should not be trying to cut calories from available foods, we should be improving the quality of the foods available that provide our calories."

Lucan SC, DiNicolantonio JJ. How calorie-focused thinking about obesity and related diseases may mislead and harm public health. An alternative. *Public Health Nutr.* November 2014;1–11. Available at www.researchgate.net. Accessed February 2, 2015.

Chemicals in Feminine-Hygiene Products

Although the US Food and Drug Administration regulates feminine-hygiene products, little research has been performed on the safety of chemicals used in them. Some chemicals damage vaginal and vulvar epithelial tissue. Others are carcinogenic or have endocrine-disrupting effects. Fragrance ingredients, parabens in personal lubricants, pesticides, dioxins in cotton used to make tampons and sanitary pads, and even tampon plastic applicators may have negative effects, according to laboratory evidence. Chemical compounds are readily absorbed by vaginal and vulvar mucous membranes. Yet menstrual product research has been a low priority in the US, according to science writer Wendee Nicole.

Because of the sensitive, permeable nature of tissue in the genital area, even "generally recognized as safe" chemicals, such as glycerin, can cause problems. Glycerin and related compounds, commonly used in aqueous-based personal lubricants, pull water out of vaginal and rectal epithelial cells through osmosis, causing irritation and destroying cells. Damaged epithelial cells have been linked to changes in vaginal flora and higher incidence of bacterial vaginosis. The cellular damage may also increase a women's risk of acquiring sexually transmitted diseases such as herpes and human immunodeficiency virus. Silicone-based lubricants have the least effect on cells, according to today's research.

Tampons are the most commonly used feminine-hygiene product. Tampon-related deaths due to toxic shock syndrome (TSS) made headlines a few decades ago. Synthetic fibers in high-absorbency tampons, sold at that time, created the perfect environment for *Staphylococcus aureus,* which produced lethal toxins. When three of the four types of synthetics were taken off the market, TSS rates declined. A few cases are still reported each year. Unlike tampons with synthetic fibers, all-cotton tampons have never been linked to TSS. Long-term effects of pesticides in cotton are unknown.

The Robin Danielson Act, a bill first introduced by Congresswoman Carolyn Maloney (D-NY) in 1999, promotes federal research on feminine-hygiene products and the chemicals that they contain. Although the bill has been voted on repeatedly (last in 2011), it has failed to pass. The majority deems it "'unnecessary and a waste of money.'"

Nicole W. A question for women's health. *Environ Health Perspect.* March 2014;12(3):A71–A75. Available at http://ehp.niehs.nih.gov/122-a70. Accessed December 4, 2014.

Dried Plums for Bones

Eating dried plums (prunes) reverses bone loss, according to animal and clinical studies. This fruit slows bone removal (osteoclast activity) and increases bone formation (osteoblast activity) and glutathione activity, according to a 2013 mouse study. Elizabeth Rendina and

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colleagues fed adult osteopenic ovariectominzed mice with either a control diet or a diet supplemented with dried plum, apple, apricot, or mango for eight weeks. Dried plum was the only tested fruit to prevent tibial bone loss as well as increase whole-body and spine bone mineral density. In addition, the dried-plum group showed increased bone formation in vertebral trabecular bone that "coincided with improved biomechanical properties, including bone strength and stiffness."

In clinical studies, dried plums have improved bone-related biomarkers and bone density. In a 2011 study led by Shirin Hooshmand, 160 osteopenic postmenopausal women were randomized into two groups. One group included dried plum (100 g/day) in their diet (about 14 half-dollar-size prunes). This amount improved bone-related biomarkers in an earlier study. Because of dried plums' laxative effect, the women were asked to reach this dosage gradually. Women in the other group ate dried apples (75 g/day), which provided a comparable amount of energy, carbohydrates, fat, and fiber. Women in both groups also took 500 mg of calcium and 400 IU of vitamin D each day. None of the women were on hormone replacement therapy or taking any other medications known to significantly affect bone metabolism.

In the year-long study, several bone markers were measured at baseline and at 3, 6, and 12 months. Data on diet, physical activity, height, and weight were also gathered at those times. The researchers assessed bone density at baseline and at 12 months using dual-energy X-ray absorptiometry. Two bone turnover markers – serum bone-specific alkaline phosphatase (BALP) and osteocalcin (OC) – declined in the dried-plum group. The decline of BALP was significant at 12 months compared with baseline. In the dried-apple group, serum BALP and OC levels increased. Tartrate-resistant acid phosphatase-5b (TRAP5b), a specific marker of bone loss, "decreased significantly in the dried plum group at 3 months and stayed at the same level at the 6- and 12-month time points." TRAP5b increased nonsignificantly in the dried-apple group. Inflammation, reflected in serum C-reactive protein, also declined in the dried-plum group but not the dried-apple group.

Both groups showed positive changes from baseline in ulna, spine, femoral neck, total hip and whole-body bone mineral density (BMD). Women in the dried-plum group had a significant improvement in ulna and spine BMD, compared with those eating dried apples. (The study design makes it impossible to parse out the effect of calcium and vitamin D. I'd like to see a control using calcium and D only and a group using plums and no Ca-D.)

Dried plums contain several nutrients known to support bone health, including magnesium, vitamin K, boron, and potassium. Moreover, polyphenols extracted from the dried plums reduced osteoclastogenesis and boosted osteoblast activity in two published studies, according to Rendina et al.

For those who are wary of dried plums' laxative effect, it may be helpful to know that a 6-month preliminary study indicates that 50 grams/day of dried plum (about 6–7 prunes) may be as beneficial as 100 grams (*FASEB Journal*; April 2014).

Hooshmand S, Chai SC, Saadat RL, et al. Comparative effects of dried plum and dried apple on bone in postmenopausal women. *Br J Nutr.* 2011;106:923–930. Available at www.researchgate.net. Accessed February 2, 2015.

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Hypofractionated Breast Irradiation

American Society for Radiation Oncology practice guidelines and the Choosing Wisely Initiative recommend fewer weeks of radiation treatment after breast-conserving surgery than is typically used for early-stage cancers. Conventional whole breast irradiation (WBI) consists of 5 to 7 weeks of daily treatment. Hypofractionated WBI uses fewer, higher-dose treatments usually given over a 3-week period. Hypofractionated WBI increases convenience, reduces treatment burden, and lowers health-care costs while offering similar cancer control to conventional WBI, according to a study by Justin E. Bekelman, MD, and colleagues.

In their 2014 study, Bekelman et al. looked at claims data from 14 commercial health-care plans (2008–2013). Practice guidelines endorse hypofractionated WBI for early-stage breast cancer patients, aged 50 and older, without axillary lymph node involvement or prior chemotherapy. The guidelines permit its use in younger women and in those with axillary lymph node involvement or prior chemotherapy. Although the use of hypofractioned WBI has increased since 2008, only 34.5% of the women aged 50 or older with early-stage cancer (endorsed group) and 21.2% of the permitted cohort received hypofractionated radiation therapy in 2013.

As expected, the shorter treatment produced cost savings. Adjusted mean total health costs in the year after diagnosis for the hypofractionated-endorsed group was $31,641 for those who used conventional WBI and $28,747 for those treated with hypofractionated WBI (difference, $2894; 95% CI, $1610–$4234; $p < .001$). Adjusted mean total health costs for the hypofractionated-permitted group were $72,860 for women treated with conventional WBI and $64,273 for those who had hypofractionated WBI (difference, $8587; 95% CI, $5316–$12,017; $p < .001$).

Partial breast irradiation with the MammoSite catheter (brachytherapy) is another alternative to conventional WBI. Like hypofractionated treatment, MammoSite brachytherapy requires shorter treatment duration and has low rates of local recurrence. Unlike WBI, MammoSite

brachytherapy has a higher risk of palpable masses (noncancerous) and telangiectasias (permanent dilation of superficial capillaries), according to a 2013 study led by Kari M. Rosenkranz.

Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA*. December 17, 2014;312(23):2542–2550. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4271796/pdf/nihms. Accessed December 27, 2014.

Rosenkranz KM, Tsui E, McCabe EB, Gui J, Underhill K, Barth RJ. Increased rates of long-term complications after MammoSite brachytherapy compared with whole breast radiation therapy. *J Am Coll Surg*. Septermber 2013;217(3). Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3808115/pdf/nihms. Accessed December 27, 2014.

Neonatal Gut Microbiota

The establishment of an infant's gut microbiome rests on a number of prenatal and postnatal factors, according to a 2014 Canadian review article. A diverse microbiome aids immune system development, protects against pathogens, and helps digest food. Some gut bacteria profiles have been linked to immune-related illnesses such as asthma, allergic disorders (e.g., atopic dermatitis, rhinitis), and chronic immune-mediated inflammatory diseases.

Contrary to expectation, babies are exposed to beneficial gut bacteria in the womb, according to recent evidence. DNA from *Lactobacillus* and *Bifidobacterium*, both of which are normal residents of a healthy gut, has been detected in placentas. *Bifidobacteria* have also been found in meconium, amniotic fluid, fetal membranes, and umbilical cord blood taken from healthy mothers and infants.

Factors that change the mother's microbiota during pregnancy affect a baby's commensal bacteria composition after birth. A woman's use of antibiotics around the time of birth (perinatal period) corresponded to delayed colonization by *Bifidobacteria* and *Lactobacillus* species in the baby (Faa G et al. *J Matern Fetal Neonatal Med* 2013;26[52]:35–43). *Bifidobacteria* and *Lactobacillus* counts were also lower in infant monkeys whose mothers were stressed during pregnancy. Reduced levels of *Bifidobacteria* and *Lactobacillus* correlate to higher risk of allergic conditions, irritable bowel, and inflammatory bowel disease.

The birth process itself is a major factor in the establishment of an infant's microbiome. The reviewers say, "A number of studies have described altered fecal or intestinal microbiota profiles in cesarean section-delivered infants beginning at 1 day after birth and persisting to 6 weeks, 6 months, and even 7 years of age." Vaginally born infants typically have more microbial diversity in their GI tract and a higher incidence of *Lactobacillus, Prevotella,* and *Sneathia* – all of which are normal inhabitants of a woman's vagina. Cesarean-delivered babies have high levels of skin microbes, less *Bifidobacteria*, and less microbial diversity. These microbiome alterations may contribute to Cesarean-delivered children's higher incidence of immunological disorders. Children born by C-section have a 20% higher risk of asthma, a 10% greater risk of developing juvenile rheumatoid arthritis, and about 40% greater risk of developing other immune defects, according to a 2014 *Pediatrics* study. These conclusions were based on data from 2 million Danish children born between 1973 and 2012.

A baby's diet also influences gut microbiota. Commensal bacteria thrive in breast-fed infants. Breast-fed infants had more than twice the number of *Bifidobacterium* cells in their stool, compared with formula-fed babies in a 2011 study. Other studies report that *C. difficile*, a GI pathogen, is more prevalent in formula-fed infants.

Investigation into the microbiome's role in human health is just beginning. "Whether the altered microbiome causes the disease or is the disease affecting the microbiome remains an issue of debate," write the Canadian reviewers. " ... future research should incorporate extended microbiota analyses, detailed nutrition assessments, and longitudinal measures of disease conditions throughout childhood."

Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH) [abstract]. *Anaerobe*. December 2011; 17(6):478–482. Available at http://www.sciencedirect.com/science/article/pii/S1075996411000333. Accessed February 2, 2015.

Munyaka PM, Khafipour E, Shia J-E. External influence of early childhood establishment of gut microbiota and subsequent health implications. *Front Pediatr*. October 2014;2:Article 109. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4190989/pdf/fped-02-00109.pdf. Accessed January 16, 2015.

Ringgaard A. Giant study links C-sections with chronic disorders [online article]. ScienceNordic. December 9, 2014. http://sciencenordic.com/giant-study-links-c-sections-chronic-disorders. Accessed January 10, 2015.

Sevelsted A, Stokholm J, Bønnelykke K, Bisgaard H. Cesarean section and chronic immune disorders [abstract]. *Pediatrics*. January 1, 2015;135(1):e92–e98. Available at http://pediatrics.aappublications.org/content/135/1/e92.abstract. Accessed January 16, 2015.

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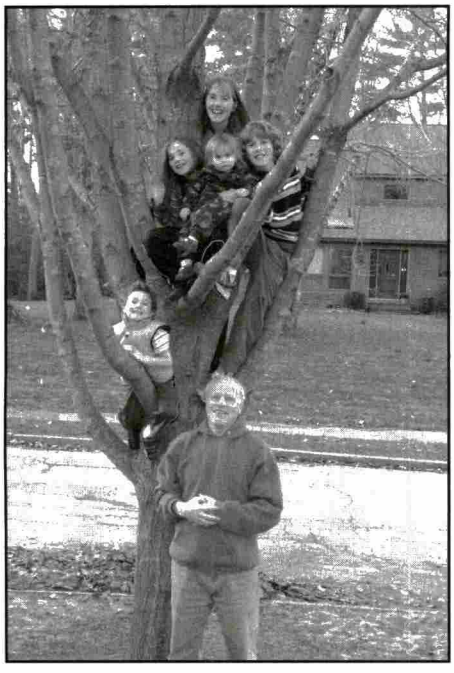

Literature Review & Commentary

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

Iron Deficiency and Female Sexual Dysfunction

Two hundred seven women (aged 18 to 49 years) with iron-deficiency anemia were asked to complete Beck Anxiety Inventory and Female Sexual Function Index questionnaires, before and after receiving iron supplementation for 3 months. Significant improvements were seen after iron supplementation in both the Beck Anxiety Inventory and the Female Sexual Function Index.

Comment: Iron deficiency can cause anxiety, which is an important factor in female sexual dysfunction. In the present study, treatment of iron-deficiency anemia was associated with significant improvements in anxiety and sexual function in women of reproductive age. Iron status should therefore be assessed in women with sexual dysfunction, and iron supplementation should be given when appropriate.

Gulmez H et al. Impact of iron supplementation on sexual dysfunction of women with iron deficiency anemia in short term: a preliminary study. *J Sex Med*. 2014;11:1042–1046.

Erroneous Basis for the Serum 25-Hydroxyvitamin D Reference Range?

One hundred ninety-eight white and African American women (aged 25–45 years) with a serum 25-hydroxyvitamin (25[OH]D) level less than 20 ng/ml (mean, 13.4 ng/ml) were randomly assigned to receive, in double-blind fashion, vitamin D (400, 800, 1600, or 2400 IU per day) or placebo for 12 months. A calcium supplement was given to increase mean total calcium intake at baseline from 706 mg per day to 1031 mg per day. Calcium absorption was measured using a single isotope method at baseline and after 12 months. After 12 months, there was no increase in calcium absorption compared with baseline in any of the groups, either in whites or in African Americans. There was no significant relationship between calcium absorption at 12 months and final serum 25(OH)D level. In an analysis of calcium absorption and serum 25(OH)D at baseline, serum 25(OH)D levels were divided into 4 groups: 0–5, 6–10, 11–15, and 16–20 ng/ml. There was no evidence of a threshold decrease in calcium absorption among the lowest groups.

Comment: In the not-too-distant past, vitamin D deficiency was defined as a serum 25(OH)D level below 10–15 ng/ml (25–37.5 nmol/L), depending on the method used to measure 25(OH)D. In recent years, the laboratory reference ranges were changed, such that vitamin D deficiency is now defined as a level below 20 ng/ml, and levels between 20 and 30 ng/ml are considered to indicate vitamin D insufficiency (mild deficiency). Using the older reference ranges, very few people are deficient in vitamin D, but using the new ranges, inadequate vitamin D status is epidemic.

The changes in the reference range were based in part on studies of the association between 25(OH) D levels and intestinal calcium absorption. It is well known that correcting vitamin D deficiency results in an increase in fractional (percent) absorption of calcium. Vitamin D sufficiency is inferred when a further increase in serum 25(OH) does not further increase fractional calcium absorption. In population studies, the average 25(OH)D level at which fractional calcium absorption no longer increased was around 30 ng/ml. However, those studies appear to have used inappropriate methods for assessing calcium absorption (such as the increase in serum calcium or in urinary calcium excretion after an oral calcium dose). Isotope methods, as used in the present study, are considered to be more reliable. In the present study, fractional calcium absorption reached a peak at serum 25(OH)D levels below 5 ng/ml.

To be sure, vitamin D has other actions in the body besides stimulating calcium absorption. However, this study and other research that I have cited in this column over the past several years support the contention that vitamin D deficiency may be far less common than the new laboratory reference ranges suggest.

Gallagher JC et al. Vitamin D does not increase calcium absorption in young women: a randomized clinical trial. *J Bone Miner Res*. 2014;29:1081–1087.

Too Much Iodine May Adversely Affect Thyroid Function

Urinary iodine concentrations were measured at a mean of 13 weeks of pregnancy in 1098 Dutch women. The median urinary iodine level was 223 μg/L, indicating an iodine-sufficient population. Thirty-one percent of the women had a urinary iodine level of less than 150 μg/L and 11.5% had a level greater than 500 μg/L. Mothers with urinary iodine levels greater than 500 μg/L had a higher risk of having a hyperthyroid newborn (3.1% vs. 0.6%; $p = 0.02$). Maternal urinary iodine levels less than 150 μg/L were not associated with newborn thyroid dysfunction.

Another study examined 146 Korean patients (mean age, 55 years) living in an iodine-replete area who had subclinical hypothyroidism (TSH of 4–20 mU/L and a normal free T4 level). Urinary iodine concentration (UIC) was measured in 82 of these patients. Of these, 20 had a UIC less than 300 μg/L and were excluded. The 62 patients with a UIC of 300 μg/L or greater were advised to restrict iodine-rich foods. After 3 to 6 months, among the 40 patients whose UIC fell to less than 300 μg/L, the median TSH level decreased from 9.0 mU/L to 4.7 mU/L ($p < 0.01$) and the median free T4 levels increased from 1.11 ng/dl to 1.18 ng/dl ($p < 0.05$). Among the 22 patients whose UIC continued to be at least 300 μg/L, no significant changes were seen in TSH and free T4 levels. Similarly, no significant changes in TSH and free T4 levels were seen in the 64 patients whose UIC concentrations were not measured and who were not given dietary advice.

Comment: Iodine is a component of thyroid hormones, and iodine deficiency can lead to goiter and hypothyroidism. However, iodine excess can also lead to thyroid dysfunction, including hyperthyroidism, hypothyroidism, and possibly autoimmune thyroiditis. The results of the 2 studies reviewed above suggest that even moderate increases of iodine intake above the Recommended Dietary Allowance raise the risk of thyroid dysfunction.

Joung JY et al. Effect of iodine restriction on thyroid function in subclinical hypothyroid patients in an iodine-replete area: a long period observation in a large-scale cohort. *Thyroid*. 2014;24:1361–1368.

Medici M et al. Women with high early pregnancy urinary iodine levels have an increased risk of hyperthyroid newborns: the population-based Generation R Study. *Clin Endocrinol*. 2014;80:598–606.

Vitamin C Helps Children of Pregnant Smokers

One hundred fifty-nine pregnant smokers were randomly assigned to receive, in double-blind fashion, 500 mg per day of vitamin C or placebo, beginning at 23 weeks or less of gestation and continuing until delivery. The newborns had pulmonary function tests at birth and at 1 year of age, and wheezing was assessed through 1 year of age. Compared with the placebo group, the vitamin C group had better pulmonary function at birth ($p = 0.01$) and a significantly lower incidence of wheezing during the first year of life (21% vs. 40%; $p = 0.03$).

Comment: Maternal smoking during pregnancy adversely affects lung development in the offspring, and results in lifelong decreases in pulmonary function and increased risk of developing asthma. In an experiment using pregnant primates, vitamin C blocked some of the adverse effects of nicotine on lung development and pulmonary function in the offspring. Vitamin C supplementation is not a substitute for quitting smoking during pregnancy. However, for women who are unable to quit, vitamin C supplementation may offer some degree of protection to the fetus.

McEvoy CT et al. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. *JAMA*. 2014;311:2074–2082.

L-Carnitine Supplementation for Women with Polycystic Ovary Syndrome

One hundred seventy women (mean age, 25 years) with clomiphene-resistant polycystic ovary syndrome (i.e., clomiphene had failed to induce ovulation) were randomly assigned to receive, in double-blind fashion, 250 mg of clomiphene citrate from day 3 to day 7 of the cycle, along with 3 g/day of L-carnitine or placebo. L-carnitine or placebo started on day 3 of the cycle and was continued ➤

➤

until the first positive pregnancy test. The ovulation rate (64.7% vs. 17.6%; $p < 0.00001$) and the pregnancy rate (49.4% vs. 1.1%; $p < 0.0001$) were significantly higher with L-carnitine than with placebo.

Comment: In this study, the addition of L-carnitine to clomiphene citrate therapy increased the ovulation rate and pregnancy rate in women with clomiphene-resistant polycystic ovary syndrome. The mechanism of action of L-carnitine is not known.

Ismail AM et al. Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;180:148–152.

Magnesium Improves Physical Performance of Elderly Women

One hundred thirty-nine healthy elderly women (mean age, 71.5 years) participating in a fitness program were randomly assigned to receive 300 mg per day of magnesium (as magnesium oxide) or no supplemental magnesium (control group) for 12 weeks. After 12 weeks, compared with the control group, the magnesium group had a significantly better mean score on the Short Physical Performance Battery ($p = 0.03$) and significantly better chair stand time ($p < 0.0001$) and 4-meter walking speed ($p = 0.006$). The beneficial effects of magnesium were more evident in participants with dietary magnesium intake below the Recommended Dietary Allowance.

Comment: This study demonstrates that magnesium supplementation can improve physical performance in healthy elderly women, particularly if their dietary magnesium intake is below the Recommended Dietary Allowance (RDA). Magnesium intake is relatively low in the United States; more than half of adults consume less than the RDA. In addition to inadequate dietary intake, risk factors for magnesium deficiency include use of potassium-depleting diuretics or proton pump inhibitors, and excessive alcohol consumption.

This study also shows that magnesium oxide can be used successfully as a magnesium supplement. Magnesium oxide has a bad reputation among some nutrition-oriented practitioners because of a study showing that it is not well absorbed. However, many other studies have found positive results in the treatment of a wide range of conditions, when magnesium was taken in the oxide form. While magnesium oxide may not be the most effective magnesium supplement, it is inexpensive and contains a higher proportion of elemental magnesium than other forms of supplemental magnesium (meaning that fewer pills will be needed).

Veronese N et al. Effect of oral magnesium supplementation on physical performance in healthy elderly women involved in a weekly exercise program: a randomized controlled trial. *Am J Clin Nutr*. 2014;100:974–981.

Calcium Supplements Are Not Harmful to the Heart

A meta-analysis was conducted on 18 randomized controlled trial (including a total of 63,563 participants) that examined the effect of calcium supplementation on cardiovascular outcomes (including myocardial infarction, angina pectoris, acute coronary syndrome, and chronic coronary heart disease) and all-cause mortality in elderly women. Overall, there were 3390 coronary heart disease events and 4157 deaths. Five trials examined coronary heart disease events, with a pooled relative risk (RR) of 1.02 ($p = 0.51$). Seventeen trials examined all-cause mortality, with a pooled RR of 0.96 ($p = 0.18$). The RR for myocardial infarction was 1.08 ($p = 0.32$); for angina pectoris and acute coronary syndrome, the RR was 1.09 ($p = 0.22$); and for chronic coronary heart disease, the RR was 0.92 ($p = 0.46$).

Comment: In 2010, a meta-analysis of 15 randomized controlled trials found that people who received calcium supplements had a statistically significant 30% increase in incidence of myocardial infarction. Those data were derived from post hoc analyses of studies (mainly osteoporosis studies) that were not designed to test the effect of calcium on heart disease risk. Findings from post hoc analyses are generally less reliable than findings from primarily analyses. In addition, as much as half of the reported increase in heart attack risk was apparently due to the fact that calcium supplements occasionally cause acute and severe gastrointestinal side effects, and that some of the study participants erroneously reported those side effects as being heart attacks. The new meta-analysis overcame that confounding factor by including only studies in which outcomes were verified by clinical review, hospital discharge record, or death certificate. The pooled results showed that calcium supplementation has little, if any, effect on heart disease-related mortality or all-cause mortality in elderly women.

Lewis JR et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. *J Bone Miner Res*. 2015;30:165–175.

Zinc Increases Effect of Antidepressant Medication

Thirty-seven patients (aged 18-55 years; mean age, 37 years; 89% female) with major depression were randomly assigned to receive, in double-blind fashion, 25 mg per day of zinc (as zinc sulfate) or placebo in addition to a selective serotonin-reuptake inhibitor for 12 weeks. Mean dietary zinc intake at baseline was 7.6 mg per day (the Recommended Dietary Allowance is 8 mg per day for women and 11 mg per day for men). The mean score on the Hamilton Depression Rating Scale was significantly lower (better) after 6 weeks (17 vs. 25; $p < 0.05$) and 12 weeks (11 vs. 23; $p < 0.01$) in the zinc group than in the placebo group.

Comment: These results indicate that supplementation with a moderate dose of zinc enhanced the effect of a selective serotonin-reuptake inhibitor in the treatment of major depression. It is not clear whether zinc worked by correcting a deficiency (dietary zinc intake is relatively low in Iran, where this study was conducted) or whether it exerted a pharmacological effect.

Ranjbar E et al. Effects of zinc supplementation on efficacy of antidepressant therapy, inflammatory cytokines, and brain-derived neurotrophic factor in patients with major depression. *Nutr Neurosci*. 2014;17:65–71.

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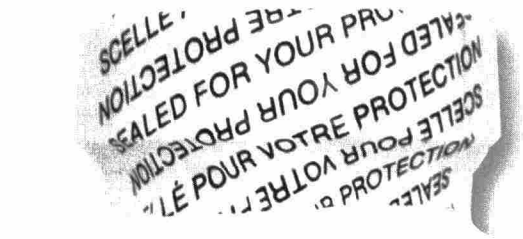

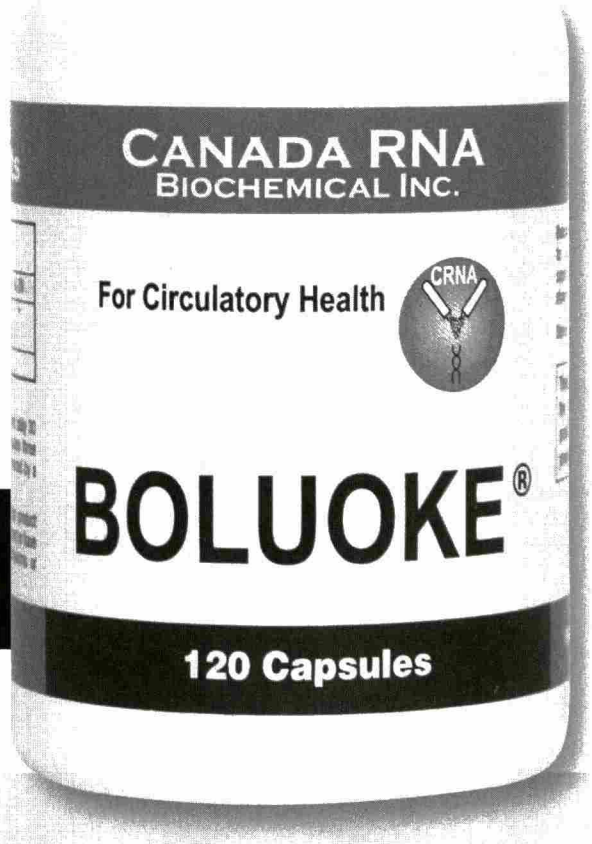

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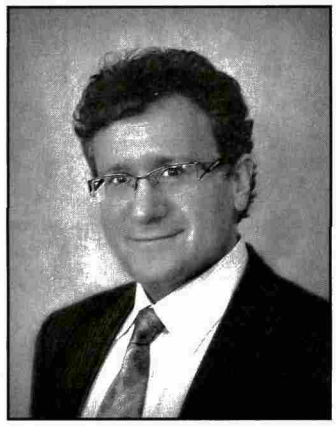

An Anti-Aging Approach to Women's Health

People are living much longer worldwide than they were two decades ago, as death rates from infectious diseases and cardiovascular disease have fallen. Collaborating researchers from more than 100 nations involved in the Global Burden of Disease (GBD) assessment report that global life expectancy for both sexes increased from 65.3 years in 1990 to 71.5 years in 2013. Women made slightly greater gains than men, as female life expectancy at birth increased by 6.6 years.

Maintaining these longevity gains requires deliberate attention, as the Centers for Disease Control and Prevention (CDC) reports that nearly 14% of US women aged 18 years and over rate their health as fair or poor. Fewer than half (45.7%) of all American women meet the 2008 federal physical activity guidelines for aerobic activity through leisure-time aerobic activity. Among women aged 20 years and up, 36.4% are obese and 32.8% have hypertension.

In this column, we review recent studies that suggest simple and effective ways to enhance women's health – with particular focus on potential natural interventions for heart disease, cancer, and stroke, the leading causes of death among women today.

GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. December 17, 2014.

Women's health [Web page]. CDC FastStats. http://www.cdc.gov/nchs/fastats/womens-health.htm. Accessed 5 Jan. 2015.

Healthful Diet for Healthy Aging

A large-scale study of women nurses reveals that eating a healthful diet reduces the odds of aging-related chronic diseases, physical impairment, and mental and cognitive issues. Cecilia Samieri and colleagues from INSERM (France) studied data involving 10,670 women, median age 59 years at the study's start, who were enrolled in the Nurses' Health Study. The researchers followed the study subjects for more than 15 years, tracking dietary habits and how well each subject aged – *healthy aging* was defined as having no major chronic diseases, physical impairment, or mental or cognitive issues. Using that definition, the team found that 11% of the women were healthy agers, with the rest aging normally. Healthy agers were found to consume a diet following the Mediterranean (abundant in fruits and vegetables) or DASH (low-salt) guidelines. The study authors conclude: "Better diet quality at midlife seems to be strongly linked to greater health and well-being in persons surviving to older ages."

Samieri C, Sun Q, Townsend MK, et al. The association between dietary patterns at midlife and health in aging: an observational study. *Ann Intern Med*. 2013 Nov 5;159(9):584–591.

Fruits and Veggies Boost Women's Cardiovascular Health

Women who eat a diet high in fresh fruits and vegetables as young adults may be far less likely to have plaque buildup in their arteries 20 years later. Michael D. Miedema and colleagues from the Minneapolis Heart Institute (Minnesota, US) studied the relationship between fruit and vegetable consumption during young adulthood and heart disease later in life. The study included 2508 participants from the ongoing Coronary Artery Risk Development in Young Adults (CARDIA) study, which is evaluating how heart disease develops throughout adulthood. Among these subjects, the team assessed the association between dietary intake of fruits and vegetables and the presence of coronary artery calcification (CAC) 20 years later. CAC scores, obtained using a CT scan, provide a direct estimate of the amount of plaque in the coronary arteries. The data revealed that women who reported consuming the most fruits and vegetables (8 to 9 servings a day for a 2000-calorie diet) in their 20s were 40% less likely to have calcified plaque in their arteries in their 40s, as compared with those who ate the least amount (3 to 4 servings a day) during the same time period. This association persisted even after researchers accounted for other lifestyle behaviors, as well as for their current-day diets, further demonstrating the role that dietary patterns at younger ages may play. The lead author submits: "These findings confirm the concept that plaque development is a lifelong process, and that process can be slowed down with a healthful diet at a young age. This is often when dietary habits are established, so there is value in knowing how the choices we make in early life have lifelong benefits."

Miedema M. The association of fruit and vegetable consumption during early adulthood with the prevalence of coronary artery calcium after 20 years of follow-up: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Presentation at: American College of Cardiology's 63rd Annual Scientific Session. March 29, 2014.

Go Bananas

Potassium-rich foods, such as bananas, may reduce stroke risk among older women. Sylvia Wassertheil-Smoller and colleagues from Albert Einstein College of Medicine (New York) studied 90,137 postmenopausal women, aged 50 to 79 years, who did not have a history of stroke at the study's start, for an average 11 years. With participants' having an average dietary potassium intake of 2611 mg/day, the researchers tracked potassium consumption and the incidence of strokes (ischemic and hemorrhagic) or deaths during the study period. Data analysis revealed that women who ate the most potassium were 12% less likely to suffer stroke in general and 16% less likely to suffer an ischemic stroke, as compared with those women who ate the least. Women who ate the most potassium were 10% less likely to die, as compared with those who ate the least. Among women who did not have hypertension, those who ate the most potassium had a 27% lower ischemic stroke risk and 21% reduced risk for all stroke types, compared with women who ate the least potassium in their daily diets. The study authors conclude: "High potassium intake is associated with a lower risk of all stroke and ischemic stroke, as well as all-cause mortality in older women, particularly those who are not hypertensive."

Seth A, Mossavar-Rahmani Y, Kamensky V, et al. Potassium intake and risk of stroke in women with hypertension and nonhypertension in the Women's Health Initiative. *Stroke*. September 4, 2014.

Omega-3s May Lower Breast Cancer Risk

Increased intakes of omega-3 polyunsaturated fatty acids may cut a woman's risk of developing breast cancer by up to 14%. Duo Li and colleagues from Zhejiang University (China) completed a meta-analysis of 26 studies involving data on nearly 21,000 study subjects, finding that women with the highest intakes of omega-3 polyunsaturated fatty acids from marine sources had a 14% reduction in the risk of breast cancer, as compared with women who had the lowest intake. Further analysis indicated that for each 0.1 g per day or 0.1% energy per day increment of intake, the risk fell by 5%. Observing, "Higher consumption of dietary [omega-3 polyunsaturated fatty acids] is associated with a lower risk of breast cancer," the study authors submit: "These findings could have public health implications with regard to prevention of breast cancer through dietary and lifestyle interventions."

Zheng J-S, Hu X-J, Zhao Y-M, Yang J, Li D. Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. *BMJ*. 27 June 2013;346.

Nature's Cancer Fighters

Abundant in flavonols and flavanones, tea and citrus fruits and juices associate with a lower risk of developing ovarian cancer. Aedin Cassidy and colleagues from the University of East Anglia (UK) analyzed data collected on 171,940 study subjects enrolled in the Nurses' Health Study and Nurses' Health Study II, examining associations between intakes of total flavonoids and their subclasses (flavanones, flavonols, anthocyanins, flavan-3-ols, flavones, and polymeric flavonoids) and risk of ovarian cancer. Food surveys were collected from subjects every 4 years. During 16 to 22 years of follow-up, 723 cases of ovarian cancer were confirmed through medical records. Data analysis revealed that participants who consumed food and drinks high in flavonols (found in tea, red wine, apples, and grapes) and flavanones (found in citrus fruit and juices) were less likely to develop the disease. In particular, just a couple of cups of black tea every day was associated with a 31% reduction in risk. The study authors conclude: "Higher intakes of flavonols and flavanones as well as black tea consumption 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*. 2014 Nov;100(5):1344–1351.

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

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Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Plant Nutrients Can Boost Metabolic Resolve

April Fools' Day is 3 months after that New Year's resolution. This is my favorite time of year to help patients succeed with diet and exercise. I reassure them that they were not foolishly ambitious on January 1, nor do they need to add yet more willpower in order to succeed. Integrative health-care practitioners can uniquely help patients improve their metabolic resolve. In this *Townsend Letter* column, I explain why I think that plant nutrients are powerful allies in diet and exercise, and how they can help patients succeed at weight loss.

Resolve to diet and exercise can be difficult to keep. Hindered by food cravings, and too tired to exercise, many cannot diet successfully. Unfortunately, the take-home message from all too many health-care encounters is, "Try harder." For example, *lifestyle medicine* is a term in growing use. While the term reminds patients to prioritize health, it also subtly shifts the responsibility of achieving health goals toward patients and away from health-care providers.

Scientific breakthroughs have provided new tools to repair underlying metabolic disturbances which make diet resolve more difficult and sometimes even unsafe. The challenge with willpower is that unrelenting food cravings usually point to a metabolism that is breaking down hard-earned muscle rather than efficiently utilizing the body's excess fat reserves. And fatigue is usually a bona fide message to reduce aerobic activity. It is therefore not surprising that strategies which diagnose and treat underlying metabolic disturbances first result in greater success.

One cause of metabolic disturbance is that patients are usually low in their body stores of plant nutrients such as resveratrol, lutein, and lycopene. While many practitioners may agree that low levels of plant nutrients are common and treatable, phytonutrient roles in promoting safe and effective weight loss are largely unrecognized.

Early in my career as the winter-over physician in Antarctica, I started appreciating the importance of "freshies," an Antarctic expression for fruits and vegetables. That's a supply-chain distance second only to delivering supplies to the International Space Station. Significantly, NASA recently designed a way to grow "freshies" on the space station to improve phytonutrient intake for the astronauts' diet.

Antarctic research scientists depend on the large team of highly skilled people who make the station operate. These support staff return seasonally, and to do so they need to pass an annual physical. Lab tests such as the cholesterol profile can prevent these vital contract workers from returning to their jobs. But living in Antarctica makes it more difficult to achieve desirable lab test levels, one example being blood triglycerides. Triglycerides are fats in the bloodstream, which, when high, increase risk of heart disease. Triglycerides don't only influence disease risk, they affect how people feel. High levels of triglycerides suggest that the metabolism has difficulty converting fat to energy. The metabolic "traffic jam" leads the body to tap other energy sources, which in turn prompts food cravings and excess calorie intake. The lack of readily available energy is associated with fatigue.

Triglyceride levels are quickly responsive to dietary changes, often in time to pass a qualifying physical. Once triglycerides respond, the scale will often follow. Emphasizing phytonutrient intake pushes refined carbohydrates out of the diet. The glycemic index of the diet becomes more favorable, and the uptake of carbohydrates into the bloodstream is more gradual. In turn, the release of insulin is more gradual and the ability to process the backlog of triglycerides improves. High triglycerides tend to inflame the liver, the organ wherein the metabolic gridlock is the most severe. Phytonutrients reduce the liver inflammation and improve sensitivity to lower amounts of

insulin. In sum, phytonutrients improve blood triglycerides in many ways, which include improved food selection, insulin sensitivity, and liver support.

Phytonutrients improve many chronic medical conditions. Most medical conditions either interfere with diet and exercise directly or require medications that can be diet saboteurs. The better controlled these conditions are, the more level the incline to diet and exercise success. For example, dieters may encounter an undesirable double-punch when prescribed corticosteroid medications increase appetite and cause the metabolism to build fat rather than muscle. Phytonutrients have been shown to improve corticosteroid-managed medical conditions including digestive disorders, allergies, asthma, and several skin conditions, to the point that less medication is required.

Research during my 2-year position at the US Food and Drug Administration in the Office of Pediatric Therapeutics underscored that medication–diet interactions in children are clinically underrecognized and that a broader array of medications affect appetite and food selection in children than is usually realized.[1,2] Both research findings imply that interventions which reduce the need for medications, especially in children, indirectly support patient efforts in diet and exercise.

So here is why I especially encourage diet and exercise "re-resolve" in April. Our metabolism "springs" into action. Phytonutrient deficiencies are especially common during winter, when we eat fewer plant nutrients. Population testing confirms that the body's plant nutrient stores are on the rise from their winter nadir by North America's April. The upsurge is especially important in overweight patients, because dieters with excess body fat average lower blood phytonutrient levels year-round. The biologic rationale is that fat-soluble plant-nutrients are sequestered in body fat, which enables fewer of them to circulate in the blood.

Another reason that April warrants a phytonutrient boost is because it's when seasonal allergies flare. While the metabolism is ready to spring into action, many patients unknowingly hinder their metabolism in April with allergy medications. Corticosteroid nasal sprays, while not as potent as oral corticosteroids, still reach the body's appetite centers, where they sabotage diet. Other allergy-sufferers take antihistamines, unaware of the medication's dehydrating and appetite-stimulating effects mediated by leptin. Phytonutrient supplements are proven to reduce allergies by stabilizing mast cells. This is exciting because in clinical practice my patients tell me that they no longer need the allergy medicines once they take phytonutrients. They are providing their metabolism with the very nutrients it needs to restore health. The side effects are improved health and metabolic resolve.

The good news for Antarctic expeditioners and all the rest of us is that "freshies" aren't the only source of phytonutrients. Often overlooked among dietary sources are sea vegetables (e.g., various kelps), spices, and herbs. The freeze-drying process is food technology poised to improve diets and some of the metabolic benefits of fresh fruits and vegetables are preserved. Some of the research has been with edamame. Those who try to make vegetarian Jell-O with freeze-dried pineapple may find that the Jell-O doesn't gel because the pineapple's bromelase enzyme remains active. A novel way to take phytonutrients is from the air, by aerosolizing propolis. Propolis is a phytonutrient blend made by honey bees which use it for repairing the hive and nourishing the brood. And integrative practitioners are well-positioned to guide patients in safe and effective use of dietary supplements.

All the best with that April resolution!

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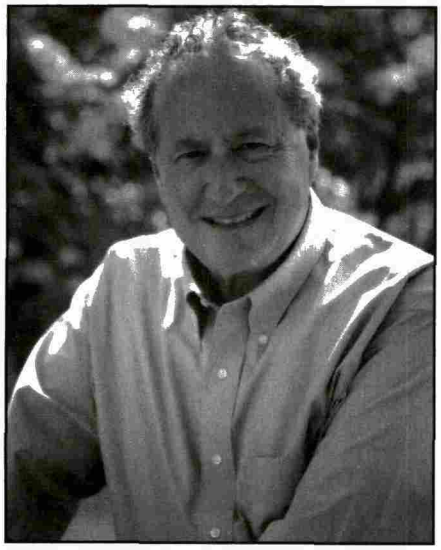

War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

Chaga Mushroom and Cancer

> He could not imagine any greater joy than to go away into the woods for months on end, to break off this chaga, crumble it, boil it up on a campfire, drink it and get well like an animal. ... Just as a dog goes to search for some mysterious grass that will save him. ...
>
> – Alexander Solzhenitsyn, *Cancer Ward*

Inonotus obliquus is the scientific name for chaga mushroom, a black-and-brown parasitic fungus, of the *Hymenochaetaceae* family. It grows as a cork-textured mass on the living trunks of mature birch trees. Other common names are clinker polypore, cinder conk, black mass, and birch canker polypore. Unlike many fungi, chaga has almost no smell or taste. In cold parts of the world, especially in regions above the 45th parallel north, chaga is abundant and can be harvested in the wild using a chisel or saw to separate it from the tree. The fungus is then powdered or cut into dice-sized chunks. One can soak it in hot water to easily make a tea. Chaga is popular in the folk medicine of not just Russia, but North America, Finland, Poland, northeast China, and Japan. In Russia, it has allegedly been used as a treatment of cancer since at least the 16th century.

Like many folk remedies of long standing, there is probably a rational core to its use. More than 20 different bioactive compounds have been found in chaga mushrooms, some of them with activity against cancer.

On a personal note, my late friend, Harris Coulter, PhD, the celebrated historian of homeopathy (*Divided Legacy*), made his living as a simultaneous translator of Russian and English. In this capacity, he got to know the famous Russian Nobel laureate and dissident Alexander Solzhenitsyn. The latter told him that while in a Soviet prison camp he had cured himself of cancer with the help of this wild-crafted mushroom. That is the incident referred to in the above quote from his book *Cancer Ward*.

There are currently 135 scientific articles in PubMed on chaga mushroom; 44 of these relate to the treatment of cancer. None of these is a clinical trial. I have repeatedly seen references to a long-ago clinical trial, but have not tracked this down. However, for the sake of completeness, I am including the following statement found at many websites:

> In a 48-patient human clinical trial in Poland in 1957, 10 patients treated with chaga showed a reduction of tumor size, a decrease in pain, a decrease in the intensity and the frequency of hemorrhaging, and a recovery accompanied with better sleep, appetite and feelings of improvement. Most of these patients were females treated with chaga for cancer of the genital organs or breast cancer.

Some of the laboratory work is quite interesting, even provocative. In January 2015, scientists in Yangling, China, isolated two lignin-carbohydrate compounds, dubbed IOW-S-1 and IOW-S-2, which have anticancer activity. A lignin is a complex chemical compound usually derived from the cell wall of plants (including trees). The carbohydrates in question bind to the lignins and make them water soluble. The substances were extracted using a hot-water method, but both water extracts and alcohol extracts have been found to have anticancer effects. (I shall say more about the extraction process in a moment.)

In the 2015 experiment, the anticancer compounds were extracted from chaga powder three times, with water at 60 °C (140 °F). Alcohol (ethanol) was subsequently used to further extract some components of the chaga. This is an important lead for anyone thinking of making their own chaga tea, for 140° F is hot, but not boiling. It is a good rule when preparing chaga tea to extract the beneficial chemicals without damaging or degrading them (as boiling water might do).

Both IOW-S-1 and IOW-S-2 can induce apoptosis (a form of programmed cell death) in cancer cells. "In addition, both carbohydrate–lignin complexes inhibited the activation of the nuclear transcription factor NF-kB in cancer cells," the authors wrote (Wang et al. 2015). NF-kB, or nuclear factor kappa B, is a key regulator of inflammation.

In the laboratory, chaga has been found to be effective against melanoma (Youn 2014), cervical (Zhao 2014), colon (Lemieszek 20119), lung and breast (Nagajyothi 2014), sarcoma (Chung 2010), lymphoma, and leukemia (Patel 2012). It needs emphasizing that – despite many anecdotes – we do not know if the same would be true in the human clinical situation. But, by all accounts, chaga is relatively nontoxic, readily available in northern forests, and nonpatentable. I believe that this accounts for the fact that no one is rushing to test its actual effects in cancer. Clinicaltrials.gov currently lists no clinical trials of *Inonotus obliquus*.

How to Make Chaga Tea

Chaga is readily available over the Internet, including at Amazon.com. One can buy it in powder form or conveniently in capsules. However, I prefer to buy it in chunks, where I can judge for myself the freshness and quality of the product. The two main sources are from Siberia and Maine. Perhaps because I once lived in the state, I favor the Maine product. Chaga is common above the area of Rangeley, Maine.

One simply takes a chunk of chaga, puts it in a container, and pours a cup of hot water over it. You then let it sit for an hour or so. You do not want to use boiling water (212 °F = 100 °C). The above scientific articles states that water at 140 °F to 160° F is best. The chaga cube can be reused twice after the initial extraction. Another scientific article indicates that of various water temperatures, 158 °F (70 °C) was optimal for the extraction of antioxidants. I tested this with a kitchen thermometer. This is not boiling but still too hot to comfortably keep your finger in for more than a few seconds.

As to alcohol (ethanol) extraction, this can be done with any good grade of commercial vodka, the stronger the better. Save the chaga chunks that have been subjected to water extraction, chop or grind them up, and put them into a vodka bath. This will get at certain beneficial compounds that cannot be extracted by water. You can then drop the desired amount of tincture into any leftover water extract. This will help keep the water extract from becoming moldy or contaminated. You can then reheat the mixture when you are ready to use it, as this will evaporate off any unwanted alcohol. The result is an extract of medicinal mushroom

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more powerful than what you are likely to buy online, at a fraction of the cost.

Why Some Docs Give Too Frequent Radiation

It is often claimed that decisions in oncology are made solely on the basis of the effectiveness of treatments. I cannot tell you how many times I have been scolded, "When there are clinical trials that prove the effectiveness of a treatment, it will quickly be implemented." However, a recent study in the *Journal of the American Medical Association* (*JAMA*) shows that this is not necessarily true. Some doctors are refusing to adopt a treatment that is proven to save patients (and society) time and money.

The *JAMA* study is remarkable not just for what it says, but for who is saying it.

The study in question does not directly concern complementary medicine, but two competing forms of radiation therapy for cancer. As background, scientists have repeatedly shown that an abbreviated course of radiation following surgery for breast cancer is as effective at preventing recurrences as a longer, more expensive course of treatment. This is now the rule in Canada. But despite this, many US doctors have failed to change their outdated practices. The reasons, the authors imply, have nothing to do with efficacy and everything to do with money. Radiation oncologists in private practice (among the best paid of all physicians) get paid more for the longer course of treatment. In many cases, they ignore the clear benefit in terms of comfort and well-being of the women involved, not to mention the needs of society to marshal scarce medical resources, and continue to subject numerous women to a longer and more arduous course of treatment (Bekelman 2014).

The senior author of the paper is Ezekiel Emanuel, MD, a former top health advisor to President Obama and current chairman of the Department of Medical Ethics and Health Policy at the University of Pennsylvania. He commented on the paper as follows: "For women as patients it's much better to have the shorter course. They get done with radiation four weeks early, and for society it's less expensive. The only person it's not good for is the radiation oncologist. I think it's a challenge for them."

In 2011 the American Society for Radiation Oncology endorsed the shorter course of radiation treatment. It remarked at the time that this short course is "equally effective for in-breast tumor control and comparable in long-term side effects," especially for women over the age of 50 who haven't had chemotherapy or do not have lymph-node involvement.

But in 2013, only about one-third of patients who were approved for a short course of treatment ("hypofractionated radiation") actually received it.

Hypofractionated radiation was significantly less expensive than the longer course of treatment: it was between 9.1% and 11.8% cheaper. The medical system could save about $4500 per patient if hypofractionation were the rule, instead of the exception.

Radiation oncologists have been very slow to adopt the less expensive guidelines. Bruce G. Haffty, MD, chairman of the department of radiation oncology at the Rutgers Cancer Institute of New Jersey, told the *New York Times*: "If a physician is doing five to seven weeks of radiation for 25 years, particularly if the physician is not a specialist and not in an academic medical center, you will be a bit leery about going to something new. Now you've got something that perhaps costs a bit less, but you wonder: Is it as effective?" (Kolata 2014).

But the equivalence of the two schedules now seems to be a matter of fact, not conjecture. In addition to inertia, some commentators are dancing around the most obvious explanation of oncologists' lackadaisical response to this data: the old way of doing things is also more profitable. If the new way were $4500 more profitable per patient, I think we would see far more doctors (especially those in private practice) quickly adopting it.

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

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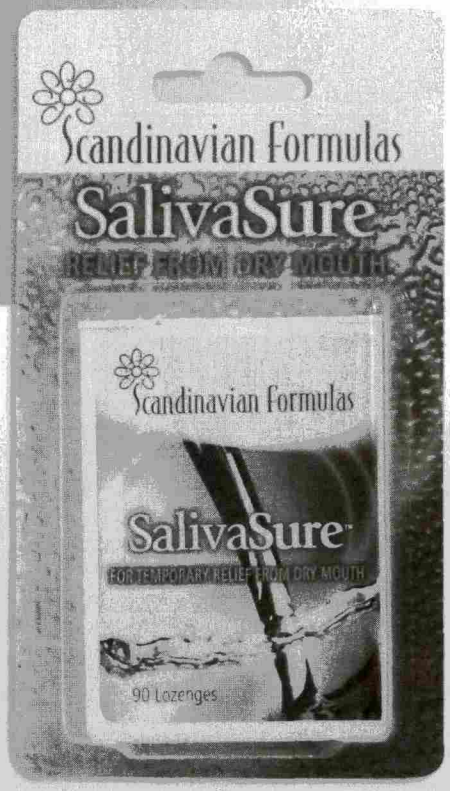

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Oral Contraceptives and Female Sexual Dysfunction

by Marianne Marchese, ND
www.drmarchese.com

Introduction

Female sexual dysfunction (FSD) is a medical condition affecting thousands of women. Women with FSD experience problems with sexual desire or response that can occur at any time in life. Several factors contribute to this condition, including physical, hormonal, and psychosocial. One common cause not often discussed is oral contraceptive pills (OCPs). OCPs have several known side effects, some of which can be life threatening. The hormonal changes induced by oral contraceptive pills can lead to female sexual dysfunction.

Female Sexual Dysfunction

Sexual desire and response in a woman is multifactorial, involving physiology, emotions, experiences, beliefs, lifestyle, and nature of relationships. Disruption of any of these components can affect sexual drive, arousal, or satisfaction. There is more than one type of female sexual dysfunction. Types include[1]:

Low sexual desire. A diminished libido, or lack of sex drive.

Sexual arousal disorder. The desire for sex might be intact, but there is difficulty or an inability to become aroused or maintain arousal during sexual activity.

Orgasmic disorder. A persistent or recurrent difficulty in achieving orgasm after sufficient sexual arousal and ongoing stimulation.

Sexual pain disorder. There is pain associated with sexual stimulation or vaginal contact.

The cause of female sexual dysfunction is often difficult to pinpoint, and more than one cause may be present. The health of a relationship, anxiety, depression, fatigue, insomnia, body image issues, and religious and cultural beliefs can all lead to issues with sexual function in women. Medical conditions play a role, especially physical conditions such as arthritis, urinary or bowel difficulties, pelvic surgery, headaches, pelvic pain, and neurological disorders. Medications contribute to FSD, as do hormones. Women often experience sexual problems postpartum, during perimenopause, and transitioning into menopause. One often overlooked link to FSD is the use of OCPs.

Oral Contraceptive Pills

Many patients and even physicians are not aware of the sexual side effects caused by hormonal contraceptives. A commonly used Web-based resource (UpToDate) does not mention mood or sexual side effects in its list of the adverse effects of oral contraception.[2] Sexual and mood side effects are one of the main reasons that women discontinue the use of oral contraceptives (OCs).

In a prospective study of 76 women in stable committed relationships, 1 year after starting OCs, only 38% continued with the original brand of OCs, 47% had discontinued the medication, and 14% had switched to another OC. Emotional and sexual side effects were the best predictors of discontinuation and switching OCPs.[3]

The mechanism of how oral contraceptives affect sexual function are well documented. Combined oral contraceptives reduce levels of androgen, especially testosterone, by inhibiting ovarian and adrenal androgen synthesis and by increasing levels of sex hormone-binding globulin (SHBG). Recently a meta-analysis was performed to evaluate these effects on women. A total of 151 records were identified by systematic review and 42 studies with a total of 1495 healthy young women (aged 18–40 years) were included in the meta-analysis. Pooling of the results derived from all the included papers showed that total testosterone and free testosterone levels significantly decreased during combined estrogen plus progestin

oral contraceptive use. Levels of SHBG significantly decreased.[4] This study also differentiated between types of oral contraceptives and found that pills containing 20 to 25 μg ethynylestradiol (EE) had similar effects on total and free testosterone compared with OCPs with 30–35 μg EE. In addition, suppressive effects on testosterone levels were not different when comparing different types of progestins.[4] However, there were differences in relation to the effect on SHBG. OCPs containing the older second-generation progestins verses the newer third- and fourth-generation progestins were found to have less impact on SHBG concentrations. Also, OCPs with lower estrogen doses (20–25 μg EE) compared with higher doses had less impact on SHBG concentrations.[4] This study suggests that OCPs with lower amounts of EE (20–25 ug) and with second-generation progestins may have less an impact on androgen levels in women.

Low testosterone in women as a result of OCP use may in part contribute to female sexual dysfunction. Testosterone deficiency is associated with many undesired effects, including diminished well-being and quality of life, mood changes, loss of energy, cognitive disturbances, interference with optimal sexual function, declining muscle mass and strength, and lowering of bone mass and bone density.[5]

The Link

It is clear that oral contraceptives affect women's hormone levels, but do these changes lead to problems in sexual function? In regard to desire, studies are mixed. In fact, one study showed that, despite the changes to androgen levels, women who used OCPs had an increase in sexual desire.[6] In this small study, 49 women were randomized into two groups to receive pills containing EE 30 mcg and levonorgestrel (LNG) 150 mcg or EE 20 mcg and LNG 100 mcg, for six cycles. Sexual function was assessed using a standardized questionnaire (Female Sexual Function Index [FSFI]). The results showed that the pill with EE30/LNG150 decreased plasma androgen levels, but there was no impairment in sexual desire; on the other hand, sexual desire score increased with in women taking the pill with EE20/LNG100.[6]

Another study using the same questionnaire had very different results. This study looked to investigate the relationship between oral contraception and female sexual dysfunction in female German medical students. This study did not measure androgen levels but looked at signs and symptoms of FSD in relation to OCP use. The FSFI was used, with additional questions on contraception, sexual activity, and other factors that may influence sexual function. 1086 questionnaires were included in the

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analyses after screening. The results showed that hormonal contraception was associated with lower total FSFI scores and lower desire and arousal scores than no contraception and nonhormonal contraception only.[7]

The majority of studies do indicate that women who use oral contraceptive pills have problems with sexual desire and libido. In a cross-sectional, community-based study of sexual function in Australian women, Davison and colleagues described that OC use was associated with a significantly lower incidence of sexual thoughts, interest, and days of sexual activity per month than reported by nonusers of OCPs.[8] Female sexual dysfunction includes more than sexual desire and arousal problems. Pain with intercourse and changes to female sexual organs are part of FSD. Oral contraceptives also play a role in sexual pain disorders.

More Than Desire

In addition to the hypoactive sexual dysfunction discussed above, OCPs have also been associated with increased incidence of sexual pain disorders such as vulvar vestibulitis (VV), causing dyspareunia and vulvadynia. A study of 138 women showed that women who have ever used OCPs have a greater risk for developing VV than women who have never used OCPs. The likelihood of developing VV was highest in women with the longest duration of pill use and in those who initiated use of OCPs at a young age.[9] The proposed mechanism linking OCPs and VV is the changes that OCPs induce in the vulva and vagina.

Oral contraceptive pills, through their interaction with hormone receptors in the vestibule, may alter the vulvar mucosa, which may in turn become more vulnerable to external exposures or irritants and eventually increase local inflammatory response, pain at touch, and dyspareunia.[10] In a study of female OCP users, the labia major thickness and vaginal introitus tissue were evaluated along with sexual function via a questionnaire. After 3 months of using an OCP containing 30 μg EE and 3 mg drospirenone, the labia minora thickness and the vaginal introitus area significantly decreased in comparison with the baseline values. The OCP use decreased the number of acts of intercourse per week, and the frequency of orgasm during intercourse. Pain during intercourse worsened after OCP use as well.[11]

Other studies confirm the link between OCP and vulvadynia and dyspareunia. In a prospective study, Bazin et al. showed that women who started taking OCPs before age 17 were 11 times more likely to develop vestibulodynia than women who had never taken OCPs.[12] A recently published case study in *Sexual Medicine* showed that 50 consecutive women developed vestibulodynia while taking OCPs. The women were treated by having them stop OCPs and by applying a compound that contained topical estrogen and testosterone to the vestibule. On average their vestibular pain dropped from 7.5 to 2 on a 10-point pain scale after 3 months of treatment. Although this was not a placebo-controlled study, the results are compelling enough to suspect that OCP use is linked to sexual pain disorders.[13]

Summary

Not all women who take oral contraceptives develop female sexual dysfunction, but many do and often go undiagnosed. Patients should be asked about sexual dysfunction during routine office visits. Clinicians should screen patients for depression and other medical conditions that might impact sexual function and address interpersonal issues such as relationship quality. For women who complain of pain with intercourse, clinicians should also complete a detailed physical examination to deterimine the exact location of pain. Other causes of sexual pain must be ruled out before assuming that the discomfort is related to OCPs. Women who believe that their OC has led to sexual dysfunction may benefit from a trial of another method of contraception.

Dr. Marchese is the author of *8 Weeks to Women's Wellness: The Detoxification Plan for Breast Cancer, Endometriosis, Infertility, and other Women's Health Conditions*. She graduated from the National College of Naturopathic Medicine in 2002. She maintains a private practice in Phoenix, Arizona, and teaches gynecology and environmental medicine at Southwest College of Naturopathic Medicine. She lectures on topics related to women's health and environmental medicine throughout the US and Canada.

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Bovine colostrum is a multi-faceted supplement which can provide welcome support to women in various phases of their lives. Outside of Leaky Gut Syndrome, the hormonal changes that occur during pregnancy, perimenopause, and menopause can take a toll on the female body. Weight gain, post-partum depression, hormone imbalance, loss of muscle tissue, and osteoporosis are just a few of the significant aspects affecting women's health for which Colostrum-LD® can help attenuate.

Post-Pregnancy

Colostrum-LD® supplementation has benefits for new mothers. It optimizes the immune system to help prevent respiratory infections, re-establishes robust bowel health, and helps metabolize residual fat deposits from pregnancy. The peptides and growth factors help enhance dopamine and serotonin uptake, thereby attenuating the post-partum blues. In addition to regular exercise and good nutrition, colostrum helps new mothers get back on their feet so they can take care of life's busy demands, especially their newborns.

Before, During, and After Menopause

Colostrum supplementation can assist women as their bodies begin the "change" by keeping those changes in check. Colostrum contains growth factors which offer a broad-spectrum boost for optimal health, tissue regeneration, and healing. The hallmark signs of aging include decreased muscle and bone mass and a loss of skin elasticity, which are manifested as loss of muscle tone, bone fractures, sagging skin, and wrinkles. This is the result of the body beginning to taper off its production of growth hormone following maturity at around age twenty. Although this is normal, it doesn't necessarily have to be. The Insulin-like Growth Factor (IGF-1 and IGF-2) and Transforming Growth Factor (TGF-α and TGF-β) in bovine colostrum have regenerative effects which extend to nearly all structural cells of the body. Bovine colostrum promotes healing and exerts the anti-aging effect by increasing IGF-1 to prepuberty levels, thereby increasing muscle mass and strength. IGF-1 also stimulates the growth and repair of DNA and RNA.

Aging changes the balance of osteoblasts and osteoclasts such that more bone is degraded than built up, leading to increased bone porosity and loss of bone strength. The decline in estrogen levels in postmenopausal women leads to an increase in osteoclasts and an acceleration of osteoporosis. TGF-beta is naturally produced by osteoblasts, and TGF-beta dramatically increases apoptosis among the osteoclasts. Moreover, osteopontin, lactoferrin, Epidermal/Epithelial Growth Factor (EGF), and IGF-2 are the dominant proteins in bovine colostrum and affect bone density in a dose-dependent manner.

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Compounding Reform: Practical Implications and the Ripple Effect Will Compounding Pharmacies Survive?

by Allison Murphy

Legislative Director, Alliance for Natural Health USA

When Congress passed the Drug Quality and Security Act in 2013, a major overhaul of the drug compounding industry was set in motion, and the US Food and Drug Administration (FDA) was given broad new powers. As the FDA releases more and more rules and regulations implementing the new law, patients, doctors, and pharmacists are starting to feel the practical implications of these reforms. Of greatest concern is the fact that the new rules have created a ripple effect, spreading to states, insurance companies, and the US Pharmacopeial Convention. Drug compounding as we know it is in grave danger.

The ability of medical professionals to tailor a treatment to an individual patient's needs – to fine-tune dosages or compound a custom formula from existing medications – is a critical part of the doctor–patient relationship. It empowers individuals to seek treatments that will be the most beneficial to their health and well-being. With compounding at risk, doctors and pharmacists will no longer be able to create medications that are the exact strength, dosage, and ingredient mix best suited to treat an individual patient. Without medical treatment customized to an individual's allergies, age, weight, medical history, and even flavor and delivery preferences, American consumers will be left with a one-size-fits-all approach to medicine.

It will be an uphill battle to effectuate change, but doctors, patients, and the entire compounding community – including my organization, the Alliance for Natural Health USA (ANH-USA) – are coming together to fight for continued access to compounded medications.

Background

In 2012, contamination at a large, industrialized plant, the New England Compounding Center, caused an outbreak of fungal meningitis, killing dozens of people and sickening many more. The NECC contamination was an isolated incident exacerbated by poor FDA oversight, but the pharmaceutical industry and the FDA used it as an excuse to attack the entire compounding industry.

Congress responded in 2013 with passage of the Drug Quality and Security Act, which created a new regulatory regime to be enforced by the FDA. In July 2014, the FDA released rules, guidance documents, and other documents implementing the new law. Compounding pharmacies are now regulated on both the state and federal level and are divided into two categories – Section 503A of the Food, Drug, and Cosmetic Act covers smaller, traditional pharmacies; section 503B covers large "outsourcing facilities."

Generally, state pharmacy boards are the primary regulators of 503A establishment; that is, state-licensed pharmacies that compound drugs. The FDA also retains some control over 503A pharmacies, regulating such areas as the adulteration or misbranding of compounded drugs, or false or misleading statements in the labeling or advertising of such drugs.

Large outsourcing facilities, on the other hand, are regulated on the federal level. They must maintain compliance with current Good Manufacturing Practices (cGMPs), complete satisfactory FDA inspections, report all adverse events, and provide the FDA with certain information about the products they compound.

Problems with the New Rules

Several sections of the new rules will hurt doctors, patients, and compounding pharmacists. The area that has the potential to be most harmful is "office use."

"Office use" is when a physician, in his or her office or other treatment area, administers a compounded medicinal preparation directly to a patient for the immediate treatment

of a problem. In these instances, a doctor would need to have a reserve supply of compounded drugs on hand without a prescription. Pharmacies might be called upon to repackage manufactured drugs to produce various compounded formulations in advance of a prescription – especially if they know they have a standing order on certain formulations.

Now the FDA is repressing office use and pharmacy repackaging. A patient-specific prescription is being required for all drugs compounded (with a narrow exception if the compounding is based on an established relationship with the patient), and the FDA will bring action against traditional compounders that do not require prescriptions. This conflicts with state laws governing the pharmacist–prescriber relationship and impinges on the doctor–patient relationship. Keeping a supply of medications for office use allows doctors to respond quickly to patients in need of treatment, ensure patient compliance, and monitor physical reactions. Limiting office use does nothing to improve patient safety and instead limits doctors' ability to do what is best for their patients.

Also troublesome is the "5% Rule." Traditional compounders (as opposed to large outsourcing facilities) are now allowed to send no more than 5% of their sales out of state. This is an arbitrary limit on the movement of compounded drugs that has no impact on the health and safety of patients. The only plausible benefit of the rule would be for large drug companies, which wish to limit access to compounded medications. Note also how nonsensical a small percentage limitation like this is. How can pharmacies possibly know how much 5% really amounts to until the end of the year? By then they may have already violated the rule!

The FDA has also asked for nominations for "bulk ingredient" lists, which will delineate what drugs may be used by traditional compounders and outsourcing facilities – and which may not. Pharmacies and medical professionals have attempted to nominate the most important compounding ingredients for the lists; however, the FDA has asked for information to be included in the nomination process that is extremely difficult to compile, especially given the limited time frame for comment.

For example, in the legislation Congress stated that to be on the approved list, there must be a "clinical need" for the bulk drug substances. The FDA interpreted this as indicating a higher standard than what a physician believes is necessary for a patient. Accordingly, FDA has asked that nominations include:

- a list of other drugs that could treat the same symptoms;
- an explanation of why a compounded drug product is necessary;
- an estimate of the size of the population that would need a compounded drug product;
- a bibliography of safety and efficacy data for drugs compounded using the nominated substance; and
- an explanation of why the drug to be compounded must be compounded using bulk ingredients instead of the FDA-approved drug product.

Ripple Effect of the New Regulations

Since the NECC incident in 2012, Congress has blamed the FDA for failing to properly oversee the facility. According to a report from the House Energy and Commerce Committee chronicling "the FDA's missed opportunities to protect public health," the FDA became aware of problems at that facility as early as 2002, a full decade before the incident, and had several opportunities to prevent the disaster that occurred. The FDA, on the other hand, has said that responsibility for the problems should be shared with the Massachusetts Public Health Department and the state's pharmacy board.

As a result, states have felt compelled to act as well, in addition to the more stringent federal regulations already noted, creating a double barrier to accessing compounded medications. For example, Georgia now requires that a specific license be on file for any out-of-state compounder shipping its product to Georgia. The license costs thousands of dollars, and is such an administrative burden that many simply refuse to ship ➤

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to Georgia rather than obtain that license. Virginia requires that any compounder who ships into the state be registered with the state Board of Pharmacy and designate a pharmacist licensed in Virginia to be in charge of compliance. North Carolina says that office use compounding is permitted – but only insofar as it conforms with federal law, which, as we note above, may be very little, or not at all.

Insurance companies are also limiting access to compounded medications. In November 2014, three compounding pharmacies filed suit against Express Scripts Inc., a pharmacy benefit manager (PBM). PBMs are companies that process prescriptions for insurance companies and corporations, and use their size to negotiate low prices with drug makers and pharmacies. Express Scripts has been denying claims for compound pharmaceutical medications, in violation of federal law – the company has blocked coverage of approximately 1000 ingredients for compounding without providing any reasonable justification.

Under federal law, a claims handler must disclose the specific reasons for a claim decision, including specific references to the health plan provisions upon which a "not covered" claim is allegedly based. Internal documents from Express Scripts revealed that it chose to deny coverage in an effort to cut spending on compound pharmaceuticals by 95%; however, letters to the patients cited spurious rationale, such as unspecified changes in the compounded medications and a lack of FDA approval for compounded medications. Other PBMs such as Optum RX, CVS Caremark, and Catamaran have also placed restrictions on compounding ingredients.

In addition, new rules from the US Pharmacopeial Convention (USP) could also threaten access to compounded drugs. The USP is a nonprofit that sets quality standards for foods, drugs, dietary supplements, and compounded medications. The USP actually predates the FDA, and the two work closely together – many USP standards have been adopted in federal law. Recently, the USP announced that it will create new standards for the handling of hazardous drugs.

The new standards are intended to protect health-care workers from exposure to hazardous drugs; however, the new standards are very aggressive and will severely affect compounding pharmacies, particularly small traditional pharmacies which will have difficulty complying. For example, the new standards would require that hazardous drugs be unpacked in negative-pressure rooms, which many facilities would not be able to build; purchasing the necessary equipment and building the additional rooms could cost hundreds of thousands of dollars. The added costs could ultimately stop many traditional pharmacies from providing compounded medications deemed hazardous, including estriol and thyroid medications. The new rules should be balanced with the actual level of risk involved, and there is no evidence that many of these drugs are hazardous to health-care personnel – there have been no incidents precipitating the need for additional regulation.

Earlier this year, the FDA announced the formation of the Pharmacy Compounding Advisory Committee, a 14-member panel that will advise the FDA on the scientific, technical, and medical issues surrounding drug compounding. However, stakeholders were given no input on the composition of the board, and nominations made by members of the compounding community were largely ignored. This means the very population who know the most about compounding will be without a voice on the committee that will govern it. This also means that the current regulatory approach will be able to proceed unchallenged.

Current Status in Congress

Fortunately, some members of Congress have remained committed to creating sound compounding policy. According to Rep. Morgan Griffith (R-VA), the FDA's treatment of office use is of "grave concern." Griffith said he will continue to work on the issue with other members such as Reps. Gene Green (D-TX) and Diana DeGette (D-CO). Senator Lamar Alexander (R-TN) has criticized the FDA for failing to communicate with doctors, patients, and pharmacists during the implementation process.

Senator Alexander is not the only member to question the FDA's actions. During last year's budget process, language was included in a Senate Appropriations Committee report stating that "oversight of FDA has not kept pace with the growth in the agency's regulatory authority or funding." Likewise, the House Appropriations Committee said it would continue monitoring the FDA's oversight of compounding pharmacies to make sure it adheres to congressional intent, which was *not* to eliminate office use or create unrealistic burdens for protecting compounded ingredients. The committee also said that state pharmacy boards should continue to have primary oversight of traditional compounding pharmacies – not the FDA.

Taking Action

In December 2014, a stakeholder group that included physicians, pharmacists, and patient advocates such as ANH-USA sent a letter to Congress and the FDA calling on lawmakers to "address the concerns with office-use and repackaged compounded medications legislatively as soon as possible so that providers

and patients can have access to these essential treatments and/or work with FDA on a responsible regulatory approach." It is now imperative that the compounding industry continue to communicate with legislators about the need for a legislative fix to halt further damaging regulations.

Congress and the FDA should examine the issue in hearings or some other public forum that would allow all stakeholders an equal opportunity to express their concerns. Hearings will also bring more transparency to the rule-making process. Many groups have also called on the FDA to reopen their regulations for public comment so that stakeholders may weigh in on the practical consequences of the regulations.

Visit www.SaveCompounding.org to get more information on compounding and find a quick and easy way to tell the FDA how the rules will affect your access to vital compounded medicine. We hope you – not to mention the doctors, patients, and pharmacists of your acquaintance – will share the link and encourage everyone in their own social networks to take action immediately.

ANH-USA: Fighting for Your Rights

At its core, the Alliance for Natural Health USA is a grassroots consumer advocacy organization. We carefully track proposed legislation, explain to consumers and practitioners how it can affect them, and offer them a means to take meaningful action. ANH-USA and its allies will continue to fight for integrative practitioners and compounded medications, carefully monitoring FDA activity and advocating for sound policy.

We work on a plethora of issues in addition to compounding, including protecting access to dietary supplements, and organic and natural foods; monitoring the Codex process; promoting GMO labeling; and protecting integrative practitioners from predatory state medical boards and private trade groups.

We invite you to subscribe to our weekly e-newsletter, the Pulse of Natural Health. It's through the Pulse that we alert our network of grassroots activists to troubling laws and regulations, and provide opportunities for direct action. This strategy works extremely well – after all, it was our grassroots activists who helped win so many concessions in the final compounding bill. To subscribe to the Pulse, please visit www.ANH-USA.org.

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The Impact of Diet and Nutrition on Ovulatory Infertility

by Aviva Romm, MD

Case Study: Ovulatory Fertility Problems

Mattie was 28 when she first began struggling with fertility issues. After 8 months of her attempting to get pregnant, a fertility evaluation led to a diagnosis of ovulatory infertility: Mattie's ovulation was inconsistent, though she had always considered her periods regular at 26 to 34 days apart. A workup was negative for medical causes of her irregular ovulation: she had normal prolactin, gonadotropins, and sex hormones. She did not have clinical features of polycystic ovary syndrome (PCOS).

For another year, Mattie tried without success to become pregnant. Another consultation with a fertility specialist revealed no major medical issues for either Mattie or her husband, and medical fertility treatments were discussed. Mattie preferred a more natural approach, so she came to me for a consultation.

Most notably, my new patient was tall and thin – too thin, in fact. At a height of 5 feet, 8 inches, and a weight of just under 120 pounds, her BMI was 17.9 – putting her in an underweight category. A careful review of her labs showed mild iron deficiency anemia, normal thyroid function, a normal female hormone panel (done on days 3 and 21 of her otherwise normal menstrual cycle), and no other problems. She had no history of pelvic infection, congenital issues, or other issues that might have led to mechanical problems with fertility. While she also had no history of an eating disorder, she described her current eating habits as erratic due to her busy lifestyle and professional commitments, and her BMI was too low (something that one might also see in an eating disorder) – another possible etiology for infertility.

A thorough review of her diet revealed that breakfast largely consisted of a cup of coffee and sometimes a pastry; lunch a vegetable salad or a fast food meal; and dinner generally no more than 4 to 6 oz. of red meat or chicken, some rice or potatoes, and a small amount of steamed broccoli or a salad. Snacks included, on occasion, a muffin, a candy bar, some nuts, or an energy bar. A second cup of coffee midafternoon was common on weekdays when she worked. She often experienced periods of what she described as "low blood sugar," which her subjective symptoms corroborated, and she often craved sugar.

My initial approach with my generally healthy but undernourished patient was to focus on optimizing nutrition and healthful weight gain, to encourage an optimal preconception diet to promote natural fertility. She was instructed to include a wide variety of healthful protein sources at each meal, including legumes, organic poultry, and low-mercury-containing fish; to increase her intake of monounsaturated fats, particularly olive oil; to add additional healthful fats such as avocado and some coconut oil to her diet; to include whole grains for complex carbohydrates; and to emphasize nuts, organic whole-fat yogurt, and vegetables with hummus for snacks.[3] She was asked to discontinue drinking coffee and decrease her sugar intake substantially. If she was in a rush and unable to make breakfast, she was instructed to make a protein shake using a pea source containing 15 grams of protein per serving. Additionally, she was started on a prenatal multivitamin and mineral supplement with methylfolate, and she was given fish oil. Her diet was enhanced with iron-rich foods, and she was started on iron chelate and buffered vitamin C to resolve anemia.

A little over 2 months later, Mattie had happily gained 8 pounds (BMI now 19.5). She was no longer anemic. She enjoyed her new dietary choices and had added light exercise – walking and yoga – to her lifestyle. At 4 months after the time we met, she conceived without additional intervention and remained on the prenatal vitamin/mineral supplement and fish oil. Mattie bore a healthy son after an uneventful full-term pregnancy and uncomplicated birth in her own home.

While elaborate supplement and botanical options are available for women struggling with infertility, remembering that food is often our best medicine is an important basis for improving fertility.

The Role of Nutrition in Fertility Problems

Currently, 1 in 6 women in the US struggles with a fertility problem. Ovulatory infertility accounts for as many as 30% of all cases of infertility. Many women prefer to avoid the expense and potential adverse effects[3]

of medical infertility treatment. Nutrition not only plays an important role in achieving pregnancy, but the mother's nutritional status at the time of conception can determine the health of her pregnancy as well as affect embryonic and fetal growth and development. In fact, placental and embryonic development is most vulnerable at the time of conception and can be influenced by maternal nutritional status.[1] For most women, making simple dietary modifications is more affordable; relatively easy compared with the effort involved in conventional fertility treatments; and, for a subset of women preferring natural options, may be more consistent with their personal beliefs about health.

Most notably, a cohort of 18,555 nurses without a history of infertility were followed for dietary habits over 8 years as they attempted to become pregnant, or became pregnant, as part of the Nurses' Health Study II (NHS).[2] Their nutritional habits were analyzed twice during the course of this study. Using a multivariate-adjusted relative risk of ovulatory disorder comparing women in the highest and lowest quintiles (confidence interval 95%, p value <0.001) the authors drew several important conclusions about dietary and nutritional patterns that may prevent, or promote, ovulatory infertility. This article is a brief review of their essential findings, which can be implemented in the treatment of women with ovulatory fertility disorders including, but not limited to, PCOS.

Weight and Fertility

Women who are either underweight or overweight are at increased risk for infertility, particularly ovulatory infertility.[2] While PCOS is typically associated with women who are overweight, it can in fact occur at any weight, as can its underlying pathophysiology, insulin resistance. The relationship between weight loss and resolution of fertility challenges in women with PCOS is well established in the medical literature. Maintaining a BMI between 18.4 and 24.4 appears to be optimal for promoting fertility and preventing or reducing insulin resistance.

Glycemic Load and the Insulin Resistance Connection

The role of insulin resistance is well established in PCOS, which is one of the primary causes of ovulatory infertility problems, and improvement in insulin resistance with weight loss in overweight women with PCOS is known to improve fertility. In the NHS, women whose diets were high in glycemic load had nearly double the risk of ovulatory infertility.[4] Glucose homeostasis and insulin sensitivity appear to be central to healthy ovulatory function and fertility.

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Micronutrient Deficiencies: Folic Acid and Anemia in Fertility Challenges

Adequate intake of iron supplements and sources of non-heme iron (i.e., plant-based sources) reduces the risk of ovulatory infertility, whereas this association is not seen with supplementation of heme iron (i.e., from animal sources).[4] Folate is important for oocyte maturation, while zinc is important for healthy ovulation and normal menstruation. Reactive oxygen species have a negative impact on oocyte maturation and ovulation, suggesting the important role for antioxidants in fertility. Poor folate status and elevated levels of homocysteine have been associated with an increased risk of fertility problems, miscarriage, and pregnancy complications, including preeclampsia.[1,5]

Protein and Ovulatory Infertility

According to Chavarro et al., a high intake of animal protein leads to a 39% greater likelihood of ovulatory infertility than does a diet primarily based on plant protein sources. Further, women with higher protein intake from plant sources (beans, legumes, nuts, seeds) were 22% less likely to experience infertility than women with lower plant protein intake.[6]

Trans Fats and Fertility

The quality of energy and sources of fats appears to be important in ovulatory infertility. Pharmacologic activation of the peroxisome proliferator–activated receptor γ (PPAR-γ) improves ovulatory function in women with polycystic ovary syndrome, and specific dietary fatty acids can affect PPAR-γ activity. According to Chavarro et al., for every 2% increase in the intake of energy from trans fats rather than from carbohydrates or omega-6 polyunsaturated fats, there was a 73% increase. Also, obtaining 2% of energy from trans fats rather than from monounsaturated fats was associated with a more than doubled risk of ovulatory infertility. Unsaturated fats may increase the risk of ovulatory infertility when consumed instead of carbohydrates or unsaturated fats found in nonhydrogenated vegetable oils.[7]

Dairy and Ovulatory Infertility

Two or more servings per day (versus 1 or less per week) of low-fat dairy products were associated with an 85% increase in ovulatory infertility risk. It appears that a protein component of dairy causes the problem, as the effects were only observed with low-fat dairy, and in fact higher intake of high-fat dairy may decrease risk.[8]

Summary: Tips for Optimizing Ovulation and Fertility with Diet and Nutrition

1. Maintaining a normal weight reduces the risk of ovulatory infertility.
2. Maintain glucose homeostasis and insulin sensitivity with a low-glycemic diet.
3. Address micronutrient deficiencies, particularly folic acid, and iron deficiency anemia.
4. Emphasize plant-based proteins over animal sources of protein.
5. Adequate intake of iron from plant sources and supplements, as well as optimal micronutrient intake, reduces the risk of ovulatory infertility.
6. Reduce trans fat intake to decrease the risk of ovulatory infertility.
7. Choose whole-fat dairy, which appears to decrease the risk of ovulatory infertility, whereas low-fat daily appears to increase the risk.

These dietary strategies form the basis of what is often referred to as a Mediterranean diet, are easily implemented by most individuals, and not only prevent ovulatory infertility but also promote long-term cardiovascular health and reduce diabetes risk.

Dr. Aviva Romm is the mother of four grown children, a Yale-trained physician specializing in integrative medicine for women and children, a midwife, an herbalist, an award-winning author, and the creator/owner of WomanWise, online courses dedicated to vitality and optimal health for women and children. An internationally respected expert in botanical and integrative medicine for women and children, she has spent nearly 30 years as a health-care practitioner and advocate for the health and environmental concerns of women and children.The recent past president of the American Herbalists Guild, a founder of the Yale Integrative Medicine program, and the author of seven books on natural medicine for women and children, including *Botanical Medicine for Women's Health*, *The Natural Pregnancy Book*, *Naturally Healthy Babies and Children*, *Natural Health After Birth*, *Vaccinations: A Thoughtful Parent's Guide*, *ADHD Alternatives* (with her husband Tracy Romm, EdD), and *The Pocket Guide to Midwifery Care*, Aviva was one of the first pioneers in natural birth and botanical medicine for gynecology, obstetrics, and pediatrics in the US.

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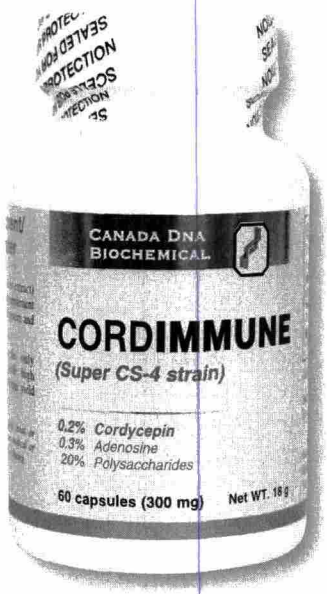

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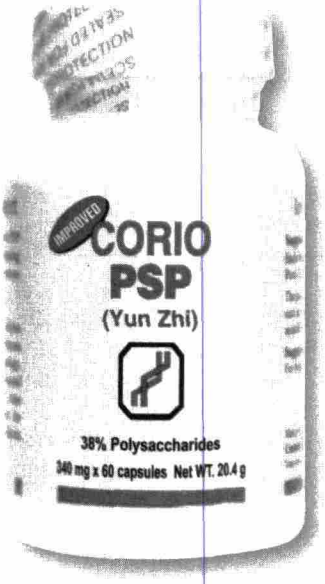

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Integrative Treatment Considerations for Cancer–Treatment Related Cognitive Dysfunction

by Lise Alschuler, ND, FABNO

Abstract

Cancer-related cognitive dysfunction – commonly referred to as "chemo brain" – is a common side effect of chemotherapy, yet many integrative practitioners are unaware that it exists in their cancer-survivor patients. Presently in conventional oncology, due to the still emerging understanding of the condition as well as due the lack of evidence-based therapies, not much is being offered to patients to either prevent or treat this cognitive dysfunction. Although there have not been any scientific studies to validate the use of an integrative approach to reversing chemo brain, given the significant impairment on quality of life imposed by this condition and the high benefit to risk ratio for indicated integrative therapies, an empiric integrative approach is warranted. This approach is buttressed by an understanding of the pathophysiology of chemo brain and utilization of targeted botanicals and nutrients that address aspects of this pathophysiology. Specifically, agents that improve connectivity, ease neurological inflammation, and enhance nerve growth factor are highly indicated in an integrative approach to chemo brain.

Introduction

Estimates indicate that up to 75% of patients diagnosed with cancer experience chemotherapy-related cognitive impairment, often referred to as "chemo brain," and in about 35% the condition persists for years following treatment.[1] In one study involving breast cancer patients, significant impairment was reported even 20 years after completion of chemotherapy, with symptoms similar to those found shortly after treatment, indicating the persistence of this chemotherapy-induced sequela.[2]

The existence of chemo brain in the medical literature is a fairly new phenomenon, as it has only been scientifically validated within the last decade.[3] Symptoms of chemo brain can include:

- memory lapses
- trouble concentrating
- taking longer to complete tasks
- inability to multitask
- difficulty remembering common words or details
- struggle learning new things

Clinically, patient self-reported symptoms consistent with chemo brain can be used to establish the presence of this condition in much the same manner that cancer patients self-report symptoms of fatigue, anorexia, and pain. Symptoms can be subtle and cognitive function may be in the normal range while functioning is still noticeably reduced. It was previously believed that cognitive changes were strictly related to psychological factors such as depression or anxiety, or cancer-related fatigue.[4] However, newer evidence refutes this assertion. In a commentary in the *Journal of the National Cancer Institute*, Karyn Hede makes a case that "chemo brain" should be called "cancer brain" because some research indicates poor cognitive function prior to treatment in patients with invasive cancers.[5] Illustrating this very point is a 2014 study which found that people diagnosed with colorectal cancer, including those with localized disease, have a higher incidence of cognitive impairment prior to receiving chemotherapy than do age-matched healthy controls (45% vs. 15%, $p < 0.001$).[6] This suggests that the presence of malignancy per se may predispose to cognitive impairment. This, in turn, creates an even greater susceptibility to the additional cognitive impairment effects caused by chemotherapy. Of note, this study also found that women were more likely to have cognitive impairment than men, and that the cognitive impairment did not correlate with cytokine levels or anxiety or depression. Hede and other experts argue that there are likely several underlying factors that may be contributing to cognitive impairment in patients diagnosed with cancer.[7]

While clinical data that involve substances – natural or pharmaceutical – to reduce or reverse cancer-related cognitive dysfunction are limited, identification of underlying pathophysiological mechanisms provides reasonable targets for a therapeutic approach.

Potential Pathophysiological Mechanisms

The proposed mechanisms for chemotherapy-induced cognitive dysfunction are numerous. The prevailing emphasis is being placed on impaired connectivity, neurological inflammation, and alterations in neuronal signaling via nerve growth factor (NGF) deficiency. A 2014 longitudinal study was the first to demonstrate reduced connectivity between regions in the brain directly

associated with multitasking, attention, and short-term memory in patients who had been treated with chemotherapy.[8] A previous 2012 longitudinal study by the same lead researcher demonstrated changes in cerebral white matter integrity after chemotherapy in patients with breast cancer.[9] As white matter mediates communication among different brain regions, a compromise in its integrity leads to changes in cognitive performance. This same effect has been observed in the cognitive decline associated with age, neurodegenerative disease, diabetes, and alcohol neurotoxicity. The connectivity tracts most affected by chemotherapy were those involved in processing speed, working and verbal memory, and attention. The mechanism of the decreased connectivity is not known, but is surmised to be the result of demyelination of white matter axons or axonal injury.

Research demonstrates that many chemotherapeutic agents can in fact cross the blood–brain barrier and cause potential harm to the central nervous system.[10] One of the effects of chemotherapy agents is elevation of pro-inflammatory cytokines.[11] Many studies have demonstrated a link between cognitive dysfunction and an increase in inflammatory markers, particularly IL-6.[12] Neuroinflammation affects neurotransmitter levels and causes direct oxidative damage to white matter and to neurons.

Neurotrophins are a family of proteins that control survival, development, and function of neurons. Specifically, neurotrophins control synaptic function and neuroplasticity and sustain neuronal cell survival, morphology, and differentiation. Neurotrophins include nerve growth factor (NGF) and brain-derived nerve factor (BDNF), among others. Neurotrophins are important to the functional integrity of neurons and are specifically associated with attention and memory, which are areas negatively affected by chemotherapy.[13] In a prospective controlled trial of patients with B-cell non-Hodgkin lymphoma, postchemotherapy cognitive impairments were more severe than in healthy controls and this impairment was associated with lower BDNF levels.[14]

Other factors that may contribute to chemo brain include oxidative damage, genetic predisposition, HPA axis damage/dysfunction, and altered blood flow. While of interest, data supporting a direct link between dysfunction in one or more of these areas and chemotherapy-induced cognitive dysfunction are still considered preliminary.

Nutritional and Botanical Considerations

While there are many natural substances that can affect proposed mechanisms underlying chemo brain, this article will focus on several agents that show particular promise and are perhaps less familiar to many integrative practitioners. Specifically, the therapeutic possibilities of lion's mane, acetyl-L-carnitine, citicoline, curcumin, and rosemary for the management of chemo brain will be discussed.

Lion's mane (*Hericium ernaceus*) is an edible medicinal mushroom that has been used in Traditional Chinese Medicine for centuries. Preclinical studies have demonstrated the ability of lion's mane extracts to increase NGF.[15] This action appears to translate clinically. A 2009 double-blind, placebo-controlled trial demonstrated that 3 g of lion's mane taken daily over 4 weeks improved mild cognitive impairment in adults aged 50 to 80.[16] Another randomized, double-blind, placebo-controlled 4-week trial of 30 females found that 2 g of powdered lion's mane reduced depression and anxiety while improving concentration.[17] Lion's mane has also been shown to have anti-inflammatory, immune-stimulatory, and other anticancer effects.[18]

The amino acid **acetyl-L-carnitine** has been shown to enhance brain function and improve memory. Acetyl-L-carnitine has neuroprotective properties and has been shown, in the presence of NGF, to activate genes involved in the response to neurotoxins.[19] Additionally, acetyl-L-carnitine normalizes neuronal concentrations of neurotrophins, further contributing to the neuroprotective effect.[20] In a randomized, placebo-controlled trial conducted in 2011, 62 patients with severe hepatic encephalopathy were randomized to receive 4 g of acetyl-L-carnitine or placebo daily for 90 days.[21] At the end of the study, there was a significant difference between the two groups in cognitive function. Additionally, 88% of the acetyl-L-carnitine-treated patients showed favorable modification of EEG vs. 72% of the placebo-treated patients.

Citicoline is a nutrient that naturally occurs in the body and is the rate-limiting substrate in the synthesis of phosphatidylcholine, a critical component of neuronal cell membranes, thereby increasing neuroplasticity, connectivity, and cognition. A 2013 clinical trial involving 349 elderly adults demonstrated that 500 mg citicoline taken twice daily for 9 months activated the biosynthesis of phospholipids in neuronal membranes, increased brain metabolism, elevated norepinephrine and dopamine levels in the central nervous system, and exerted neuroprotective effects during hypoxia and ischemia.[22] A 2012 study showed that 60 healthy women aged 40 to 60 who took 500 mg citicoline had significantly improved attentional performance compared with placebo.[23] A 2008 study utilized magnetic resonance spectroscopy to confirm that both 500 mg and 2000 mg doses of citicoline given to 16 adults resulted in improved frontal lobe bioenergetics and phospholipid turnover. This study found that citicoline improves cognition by increasing essential phospholipid membrane components needed to synthesize and maintain cell membranes in the frontal lobe. Interestingly, the lower dose of citicoline exerted changes of a greater magnitude than did the higher dose.[24]

While many clinicians may not think of **curcumin** as a brain supportive botanical, its anti-inflammatory affects make it an appropriate herb for this population. A 2008 literature review of curcumin and Alzheimer's disease highlighted many mechanisms underlying its observed cognitive enhancement. Notably, curcumin exerts anti-inflammatory effects, specifically downregulating IL-6, IL-1, and TNF-alpha, all of which have been linked to impaired cognition. In addition, curcumin exerts antioxidant actions, decreases microglia formation, chelates metals, provides neuronal protection,

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and decreases amyloid-beta plaques.[25] A 2014 animal study showed that curcumin reduced inflammation linked to poor cognition, supported axonal regeneration, and enhanced BDNF.[26] Human studies have demonstrated an antidepressive effect of curcumin, with a daily dose of 1000 mg showing equivalent effectiveness to 20 mg fluoxetine for individuals with major depressive disorder.[27] While depression is distinct from chemo brain, this study demonstrates the clinically relevant neurological activity of curcumin.

Rosmarinic acid from **rosemary** has been show in animal models to prevent lipid peroxidation and to prevent oxidative damage in the brain.[28] The compound 1,8-cineole from rosemary has also been shown to benefit brain health. A 2012 study involving 20 healthy volunteers demonstrated that the participants who had the highest 1,8-cineole concentrations from the aroma of rosemary also had the best cognitive performance.[29] This is consistent with similar results from a 2003 study showing that rosemary aromatherapy significantly enhanced cognitive performance and working memory.[30]

There is often mention of ***Gingko biloba*** when it comes to conversations about enhancing cognition. While studies involving general cognition are positive, there was one study in 2012 specifically involving patients diagnosed with breast cancer who had been on chemotherapy. In that study, a dose of 60 mg twice daily of *Ginkgo biloba* showed no benefit in cognitive performance.[31]

Other Considerations

Research demonstrates that increasing oxygen to the brain can facilitate repair. Hyperbaric oxygen therapy (HBOT) administers pure oxygen in a pressurized chamber. HBOT has been primarily utilized for wound healing and decompression sickness, a hazard of scuba diving. It may also help repair brain damage. Preliminary research primarily involving traumatic brain injury demonstrates that HBOT induces neuroplasticity that repairs impaired brain function.[32] The same neurological improvements in neuroplasticity were also seen in post stroke patients who utilized HBOT.[33] Presently HBOT is not a recognized treatment for cancer-related cognitive dysfunction; however, the potential efficacy is intriguing.

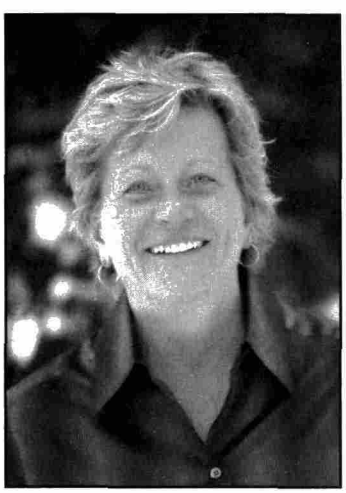
Because chemo brain can significantly affect quality of life in some patients, referral to a psychotherapist may be beneficial. Cognitive behavior therapy (CBT) is a blend of cognitive and behavioral principles to help patients deal with dysfunctional cognitive processes and maladaptive behaviors. CBT can be especially effective in cases where depression and anxiety are present.[34]

In addition to psychotherapy and CBT, patients may benefit from speed of processing training as seen in brain fitness software programs. In one study, immediate and delayed memory was improved significantly compared with those who did not go through the brain fitness training.[35]

Finally, long-term meditation practitioners have thicker callosal regions, which leads to greater connectivity.[36] Brain mapping has in fact demonstrated enhanced structural connectivity in meditators compared with controls throughout the entire brain.[37] Certainly, meditation would be a solid component of a self-care plan for individuals with chemo brain.

Conclusion

Presently, conventional medicine provides few options for patients who are experiencing chemo brain. After carefully considering potential underlying functional issues affected by chemotherapy – specifically brain connectivity, neurological inflammation, and nerve growth factor levels, integrative practitioners can work to rebuild greater cognitive function through a combination of targeted brain botanicals and nutrients such as lion's mane mushroom, acetyl-L-carnitine, citicoline, curcumin, and rosemary. Recommending HBOT, CBT, brain-building games, and meditation may also prove valuable for some of these patients. These treatments certainly do not represent an exhaustive list of cognitive-enhancing therapies. The most important take-away is to ask patients who have completed chemotherapy about their cognition. If cognitive challenges are present, integrative practitioners have a myriad of strategies to offer to these patients.



Dr. Lise Alschuler received her ND degree from Bastyr University in 1994 and is board certified in naturopathic oncology. She is past president of the American Association of Naturopathic Physicians and was a founding board member of the Oncology Association of Naturopathic Physicians. She is the coauthor of *The Definitive Guide to Cancer: An Integrative Approach to Prevention, Treatment and Healing*, now in its 3rd edition (Random House, 2010) and *Five To Thrive: Your Cutting-Edge Cancer Prevention Plan* (AIM Publishers, 2011). She, along with her coauthor Karolyn Gazella, have created www.FiveToThrivePlan.com, a multimedia website dedicated to sharing information about integrative cancer prevention and treatment. They also cohost a daily radio show, *Five To Thrive Live!* on www.w4CS.com, which provides listeners with tools for living healthier lives in the face of cancer.

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What Is Triple-Negative Breast Cancer?

by Barbara MacDonald, ND, LAc

Two out of three breast cancers are ERPR-positive, meaning that they have receptor sites that are sensitive to estrogen and progesterone.[1] About 20% of breast cancers are stimulated by a protein called human epidermal growth factor. These are called HER2-positive. There is a less common type of breast cancer that is not sensitive to, or stimulated by, estrogen, progesterone, or HER2. These are called *triple-negative breast cancer* (TNBC), and they make up approximately 15% of all invasive breast cancers diagnosed in the US.[2]

While an increasing number of studies are being done on TNBC, there are still many unanswered questions. A few years ago, I began seeing more and more women with TNBC in my practice. However, rates of TNBC actually went down from 2006 to 2010.[3] This article explains what is known about TNBC, who tends to get it, its risk factors, prognosis, conventional treatments, and the few data known about natural medicines that have been studied to confront it. It is my hope that more studies will illuminate the nature of this less common and more aggressive form of breast cancer.

The Pathology of Triple-Negative Breast Cancers

TNBC is considered a more aggressive type of breast cancer. It is typically characterized by a ductal histology, high grade, high proliferation, and mitotic rates. It is associated with poorer disease-free survival rates regardless of stage at diagnosis.[4] TNBC has a higher likelihood of local recurrence, especially when multiple nodes are positive. The risk of recurrence in patients with TNBC is higher in the first three years compared with those with the hormone-positive/HER2-negative type.[5] There are higher rates of distant metastasis to the lung, liver, and brain than non-TNBC and lower rates of metastasis to the bones.[6] Rates of BRCA gene mutations tend to be high among women with TNBC, particularly when diagnosed at a young age.[7]

It is only in the last few years that pathologists began characterizing breast cancers by their molecular subtypes. In order to delineate each subtype through gene-expression profiling, a new classification system was created. The most common type of breast cancer is called *luminal A*, which is ER-positive and/or progesterone-positive, HER2-negative. *Basal-like* breast cancers are ER-negative, PR-negative and HER2-negative, cytokeratin 5/6-positive, and/or epidermal growth factor receptor-positive.[8] This is helpful for research studies; however, it leaves room for confusion when discussing TNBC. Approximately 75% of TNBCs express basal markers.[9] Basal-like breast cancers are triple-negative, but not all TNBCs are basal-like.

Epidemiology of Triple-Negative Breast Cancer

Black women of diverse backgrounds are three times more likely than non-black women to have TNBC, regardless of age or weight. In the US, TNBC makes up 15% to 20% of the total invasive breast cancers. The prevalence of TNBC among white Americans is 10% and among African-Americans is 33%. The total number of cases of TNBC globally is approximately 170,000.[10] The prevalence of TNBC in Ghana, however, is 82% – the highest percentage of breast cancers of this subtype globally.[11] The incidence of TNBC, as a particularly aggressive type of breast cancer, may contribute to the lower survival rates among women of color.

Younger age, premenopausal status, increased parity, high histological grade, and advanced disease have been associated independently with TNBC.[12]

Genome studies identified 25 known breast cancer susceptibility *loci* as risk factors for TNBC.[13] Among them, there is an association with CYP2C19 deletion, a single nucleotide polymorphism related to estrogen catabolism.[14] Immune signatures vary among those with TNBC as well. A cytokine known as IL-5, which plays a role in certain allergic and inflammatory conditions, is particularly high among premenopausal women with TNBC.[15]

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Triple-Negative Breast Cancer

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We have also learned from studies of Chinese women, with early-stage primary TNBC, that having type 2 diabetes (T2DM) increases one's chances of local recurrence and metastasis (from 4.6% in the non-T2DM group to 23% in the diabetic group). The 2-year survival rates among TNBC patients without diabetes was 97% compared with 78% in the diabetic group.[16]

Etiology of TNBC

The risk factors that contribute to triple-negative breast cancer are varied and not yet fully understood. Associations between TNBC and weight, menopausal status, parity, breast-feeding, cigarette smoking, and alcohol have all been studied – most with conflicting results.

Weight

Being overweight or obese increases the risk of breast cancer in general. However, among studies of triple-negative breast cancer, the results are contradictory. TNBC incidence was studied within one white, socioeconomically deprived population in West Virginia. TNBC occurred more frequently among younger women, with later stage at diagnosis, and was associated with obesity.[17] Another study found weight to be a factor in the development of TNBC among premenopausal women.[18] While these and other studies did find this association between menopausal status, weight, and TNBC, another found the opposite among African-Americans. Stead et al. reported that TNBC was equally common in black women diagnosed before and after age 50, and who were obese and nonobese. Considering all patients in the study, as body mass index increased, the proportion of TNBC decreased.[19]

Parity and Breast-Feeding

Parity and nursing seems to affect one's risk of TNBC. One study author determined that TNBC cases tended to be in women who were younger at diagnosis and African-American and more likely to have not breast-fed if they had three or more children.[20] In another study, compared with non-TNBC cases, women with TNBC had a shorter duration of nursing each child and a higher parity.[21] Among participants in the Women's Health Initiative, never having children was associated with decreased risk of TNBC but increased risk of ER-positive breast cancer. Among those who had children, the more births, the higher the risk of TNBC.[22]

Oral Contraceptive Use

Studies reporting an association between TNBC and use of oral contraceptives are varied as well. The author of one such study found that using birth control pills for more than 1 year was associated with a 2.5-fold increased risk of TNBC and no increased risk among those with non-TNBC.[23] Another study found no such risk association.[24]

Cigarette Smoking and Alcohol Consumption

According to a study published using the Women's Health Initiative, cigarette smoking is not associated with risk of TNBC. Alcohol use was found to reduce the risk compared with never alcohol use among postmenopausal breast cancer patients. However, both exposures increased the risk of ER-positive breast cancer.[25]

BRCA Gene Mutations

Seventy-five percent to 80% of BRCA1-associated breast cancers are basal-like TNBCs. One study of 469 women with TNBC found that 31% had a BRCA mutation, 106 with BRCA1 and 32 with BRCA2 mutations. The rates of TNBC among those with BRCA mutations decreased with age – from 44% among those diagnosed before age 40 compared with only 13% of those in their 60s who were BRCA-positive with TNBC.[26]

Conventional Treatments of TNBC

Conventional treatment of hormone sensitive (luminal A) breast cancer is well established and has specific guidelines based on well-established criteria. This is not yet the case for triple-negative breast cancer. Due to a lack of research on this type of cancer, there are no established guidelines for the treatment of TNBC.

Surgical recommendations currently follow the same guidelines as non-TNBC unless the patient also has a BRCA gene mutation. It is recommended, however, that patients remember that there is a higher likelihood of local recurrence in the first 3 years than in those with non-TNBC.

To date, there are no FDA-approved single-target therapies for TNBC. In general, oncologists recommend chemotherapy even if the tumor is small and node negative. This is partly because of the higher risk of spread to internal organs and partly because TNBC responds very well to chemotherapy. The studies on which chemotherapy agent(s) work best, however, are limited.

Future studies appear to be targeting the five subtypes of TNBC based on the signaling pathways unique to each. Some authors recommend molecular testing prior to choosing chemotherapy.[27] TNBC responds better to chemotherapy administered

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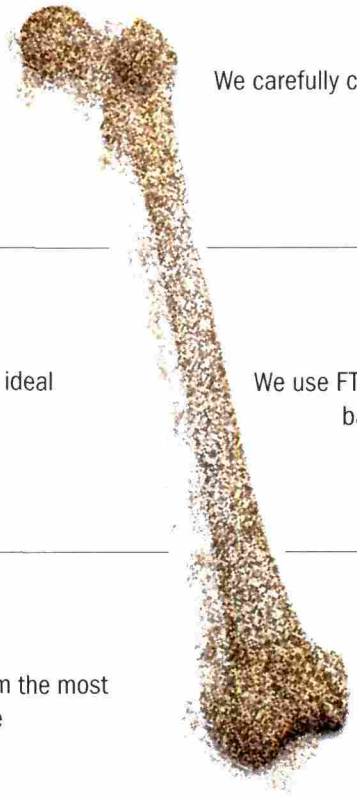

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prior to surgery (neoadjuvant) than other breast cancer subtypes. Having neoadjuvant chemotherapy has been found to induce a pathological complete response in about 30%, which means that the chemotherapy resolved any evidence of the cancer by the time of surgery.[28] Those who reached pathological complete response correlated with better prognosis in all the neoadjuvant trials.[29] It was also found that among premenopausal women with TNBC, those who were 35 years or younger more often achieved a pathological complete response to neoadjuvant chemotherapy.[30]

TNBC, like luminal A breast cancer, has been identified as sensitive to taxanes and anthracycline chemotherapeutic drugs. Standard Adriamycin, Cytoxan, followed by Taxol (AC/T) are often prescribed. More recently, it has been observed that Cytoxan and Taxotere are being combined. Platinum agents are effective in TNBC patients with BRCA1-gene mutation, either alone or in combination with poly-adenosine-diphosphate polymerase-1 inhibitors. Combinations of ixabepilone and capecitabine have added to progression-free survival (PFS) without survival benefit in metastatic TNBC.[31] The 2013 San Antonio Breast Cancer Symposium reported an improved outcome when veliparib and carboplatin were added to standard AC/T chemotherapeutic regimen.[32] Lastly, it was found that those who began chemotherapy within 30 days after surgery had better overall survival than those who waited longer to start chemotherapy.[33]

There are no established guidelines for the prescription of radiotherapy among those with TNBC. Standard indications for radiation therapy apply. Unlike those with estrogen receptor-positive breast cancer, who are offered oral medications (to block hormones) after chemotherapy and surgery, there are no post-chemo oral drug therapies recommended for those with TNBC.

Three conventional medications that are used for other diseases have been studied in vitro with TNBC, however. Metformin, an antidiabetic drug, has been found to selectively kill TNBC cell lines.[34] In addition, a proton pump inhibitor used for gastroesophageal reflux,

esomeprazole, suppresses growth of TNBC cells independently while sensitizing cells to doxorubicin (Adriamycin).[35] Finally, early in vitro and animal studies found that aspirin may play a role in the fight against TNBC as it slows the growth of TNBC cell lines and reduces tumor growth in mice.[36,37] However, in a retrospective look at breast cancer patients, it was found that regular aspirin use was not associated with any protection from developing TNBC.

Finally, 12% of women with metastatic estrogen/progesterone receptor-negative breast cancer tested positive for androgen receptors in one study. Twenty-one percent remained stable for at least 6 months in response to treatment with an antiandrogen drug, called bicalutamide, commonly used for prostate cancer. All but one of these were HER2-negative.[38]

Natural Therapies for TNBC

Several natural therapeutic agents have shown promise in retarding the growth of TNBC cell lines in vitro and in animals. The following natural therapies provide us with tools to consider in prevention of recurrence strategies:

- Those with the triple-negative breast cancer phenotype have the lowest average **vitamin D** levels and the highest percentage of patients who are vitamin D deficient.[39] Vitamin D given to a mouse model suppressed multiple proteins that are required for survival of triple-negative/basal-like breast cancer cells.[40]
- A product called **BreastDefend** that contains medicinal mushrooms (*Coriolus versicolor, Ganoderma lucidum, Phellinus linteus*), medicinal herbs (*Scutellaria barbata, Astragalus membranaceus, Curcuma longa*), and purified biologically active nutritional compounds (diindolylmethane and quercetin) was found to prevent breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer.[41]
- **Melatonin** showed effectiveness in reducing tumor growth and cell proliferation, as well as in the inhibition of angiogenesis in TNBC-induced mouse model.[42]
- **Silibinin**, given orally from the milk thistle plant, significantly suppressed tumor volume in a TNBC mice model.[43]
- **Epigallocatchin-3-gallate** (EGCG), from green tea, induces apoptosis and inhibits cell proliferation and migratory behavior of TNBC cells.[44]
- **Curcumin** induces apoptosis and inhibits the proliferation of TNBC cells.[45]
- **Ginseng** sapogenins are potent inhibitors of MDA-MB-231 human TNBC cell lines.[46]
- **Piperine**, an alkaloid from black pepper, inhibits the growth and motility of TNBC and enhances radiotherapy in vitro.[47]
- **Omega-3 polyunsaturated fatty acids** have a pronounced inhibitory effect against triple-negative basal breast cancer cell lines in vitro.[48]

Conclusion

Information about triple-negative breast cancer is lacking in general. It is reassuring, however, that the interest in studying TNBC appears to be high. The most interesting research, to me, is among those studying individualization of treatment based on gene-expression profiling. Until more information is available, I recommend that those with TNBC get an opinion from an oncology facility in a major metropolitan area. I encourage patients to request genetic testing from their oncologist and be open to neoadjuvant chemotherapy and mastectomy if recommended.

Look for an experienced, licensed, naturopathic physician in your area to help during treatment to reduce side effects and negative interactions between drugs and natural therapeutics. Complementary care providers can also offer strategies for prevention of recurrence. These range from specific dietary and fitness recommendations to individualized treatment plans including vitamins, minerals, and botanical medicines found to reduce the risk of recurrence of breast cancer.

To find experts in your area, go to the American Association of Naturopathic Physicians ➤

The 4th edition of *The Breast Cancer Companion: A Complementary Care Manual: The Practitioner's Guide to Support Women through Conventional Cancer Treatment*, will be available soon. This well-referenced text has been edited cover to cover by specialists in the field of conventional and naturopathic oncology. This clinical text provides details on what patients experience from diagnosis through the end of treatment, followed by a new section on prevention of recurrence strategies, as well as up-to-date research on complementary naturopathic therapeutics to limit side effects and promote healing. For advanced notice regarding publication date, e-mail Barbara MacDonald, ND, LAc, at drbarbmacdonald@yahoo.com.

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(naturopathic.org) or the Oncology Association of Naturopathic Physicians (oncanp.org). For more information on triple negative breast cancer in general, go to tnbcfoundation.org.

Notes

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PCOS: A Common Endocrine Disorder

by Pamela W. Smith, MD, MPH, MS

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age worldwide. It affects 10% of women in the US and accounts for 75% of the women with amenorrhea. PCOS also accounts for 85% of women with androgen excess and hirsutism.[1–12]

For a diagnosis of PCOS, two of the following three criteria must be met: oligoovulation and/or anovulation, clinical or biochemical signs of excess androgen activity, polycystic ovaries on ultrasound (greater than or equal to 12 follicles 2–9 mm in size or the volume is greater than 10 mL).[13,14]

Symptoms of PCOS commonly begin in the teen years. The following are signs and symptoms of PCOS[15–27]:

- obesity or the inability to lose weight
  - Weight gain is usually around the waist as opposed to overall weight gain.
- irregular or absent menstrual cycles
- infertility and/or recurrent miscarriages
  - Infertility affects 75% of women who are obese.
- hirsutism
  - 40% of hirsute women who have normal cycles are anovulatory.
  - Hirsutism is present in 70% of women in the US and is much less common in women in Japan who have PCOS.
- oily skin and/or acne
  - Acne is seen in 1/3 of patients.
  - Hirsutism and acne are present in 70% of women with PCOS and 10% of women without PCOS.
- acrochordons (skin tags)
- acanthosis nigricans
- depression/irritability/tension
- gray-white breast discharge
- sleep apnea
- pelvic pain
- thinning scalp hair
- hypertension
- possible epilepsy connection
  - Women with epilepsy have a 10% to 26% higher risk for PCOS than other women.

There are numerous lab abnormalities commonly associated with PCOS:

- high testosterone and other androgens such as androstenedione
- elevated insulin level/insulin resistance
- elevated LH:FSH ratio (elevated LH and decreased FSH)
- decreased sex hormone binding globulin (SHBG)
- abnormal lipid profile
- elevated DHEA levels
- high estrone

All of the etiologies of PCOS are not yet known. Scientists believe that PCOS has a hereditary component.[28–30] In fact, 40% of women with PCOS have a sister with PCOS and 35% of women with PCOS have a mother with the disease.[31,32] There is some suggestion in the medical literature that women with PCOS are born with a gene that triggers higher than normal levels of androgens and/or insulin.[33,34] Furthermore, studies have shown that the high levels of testosterone and insulin in patients with PCOS are linked through a gene called follistatin.[35] Follistatin in the body plays a role in the development of the ovaries and is also needed to make insulin. Likewise, women, overweight or not, who have this disease process have both a higher rate of insulin resistance and hyperinsulinemia than controls.[36] High insulin levels are correlated with a decrease in SHBG, which increases the level of circulating testosterone.[37,38] Insulin also works with luteinizing hormone (LH) to increase androgen production in the ovarian theca cells.[39] Looking further at a possible hereditary component to PCOS, women with the disease tend to have a hyperactive production of CYP17 enzyme that is responsible for forming androgens from DHEA-S at those sites. This mechanism is further exacerbated when the patient is obese.

About half of the women with PCOS have elevated DHEA levels.[40,41] High DHEA is due to stimulation of ACTH produced by the pituitary gland, mainly due to stress. The excessive DHEA is then converted into androgens via adrenal metabolism. This contributes to high androgen levels in PCOS. High testosterone levels correlate to the high LH levels. Subsequently, high androgen levels in the ovary inhibit follicle stimulating hormone (FSH) which then inhibits the development and maturation of the follicle.

In addition, the metabolism of estrogens changes by way of the 2-hydroxylation and 17-alpha-

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oxidation pathways which are decreased. Estrogen levels elevate due to the peripheral aromatization of androstenedione. This process then results in estrogen dominance due to the over production of estrogens.[42,43]

Skin and adipose tissue are also postulated to contribute to the etiology of PCOS. Women who have hirsutism have an elevated sensitivity to androgen activity in the skin, so they may develop abnormal patterns of hair growth. Aromatase and 17-beta-hydroxysteroid activities are increased in the fat cells, and peripheral aromatization increases with the increase in weight.

Toxicities also play a role in the causation of PCOS. Phthalates, bisphenol-A, cadmium, and mercury toxicities have all been shown to be related to PCOS. These substances are associated with being possible endocrine disrupters which alter hormones and cause anovulation, increase the risk of developing insulin resistance, and hyperandrogenemia.[44]

The imbalance in the hypothalamic-pituitary-ovarian axis that occurs in PCOS is part of the etiology of the disease. Twenty-five percent of women with PCOS have hyperprolactinemia. [45] The high prolactin levels are due to the abnormal estrogen negative feedback from the pituitary. Furthermore, elevated prolactin can contribute to high estrogen levels.

Stress may be a major contributing factor to PCOS.[46] Studies have shown that many women with the condition cannot process cortisol effectively, which leads to elevated cortisol levels in the body.[47] When women are under stress, too much prolactin may be released. This may affect the ability of the ovaries to produce the right balance of hormones.[48,49]

Hypothyroidism may also be a cause of PCOS. One study of teenage girls with PCOS showed that on ultrasound, the ovarian cysts resolved when their hypothyroidism was treated. LH levels also decreased.[50] Another trial showed that when women with hypothyroidism were given levothyroxine alone or with clomiphene citrate and/or dexamethasone, ovulation was normalized.[51] Furthermore, a study of women with PCOS found that 27% of them had elevated thyroid antibodies and 42% had a hypoechoic pattern on thyroid ultrasound which was consistent with autoimmune thyroiditis. Women with PCOS were found to have a prevalence of autoimmune thyroiditis that was more than three times higher than controls who did not have PCOS.[52]

It is important when evaluating a patient for PCOS to consider the following differential diagnosis[53,54]:

- hypothyroidism
- hypothalamic amenorrhea
- Cushing's syndrome
- congenital adrenal hyperplasia
- ovarian/adrenal tumors
- hyperprolactinemia
- premature ovarian failure

PCOS is a risk factor for the development of other major diseases such as diabetes, heart disease, hypertension, infertility, hormone-related cancers, and obesity.[55–60]

If the patient has PCOS, this is a risk factor for the development of diabetes; in fact, she is seven times more likely to become diabetic.[61,62] Likewise, about half of all women with PCOS have insulin resistance.[63] Some studies suggest that women with PCOS who have irregular cycles or no cycles may have double the risk of developing diabetes.[64] The risk of developing diabetes in patients with irregular cycles increases even more if they are obese.[65] Furthermore, the risk of getting diabetes is also increased in patients with PCOS who are not overweight or insulin resistant. [66]

Women with PCOS have an increased risk of developing heart disease when compared with women without PCOS.[67–69] Up to 70% of women in the US with PCOS have dyslipidemia.[70] Women with PCOS frequently have elevated total cholesterol, LDL, and triglycerides. They also tend to have low HDL and apoprotein A-1 levels.[71–76] Furthermore, patients with PCOS also tend to have impaired fibrinolysis as evidenced by elevated circulating levels of plasminogen activator inhibitor. This is associated with hypertension and atherosclerosis. Moreover, women with PCOS have a 7-fold risk of having an acute myocardial infarction.[77] Also, homocysteine levels may be increased in patients when they have PCOS; as well, women with this disease process tend to have higher than usual C-reactive protein (CRP) levels.[78,79] Just as interestingly, women with PCOS frequently have decreased total antioxidant status and increased oxidative stress.[80] These patterns may be some of the contributing causes of heart disease in women with PCOS.

Women with PCOS have 4 times the rate of hypertension as those who do not have the condition.[81] Insulin resistance and hyperinsulinemia raise blood pressure.[82] High levels of insulin correlate with low sodium in the urine. This leads to an increase in water retention, which makes it harder for blood to flow through the circulatory system, consequently leading to an increase in blood pressure. High insulin levels also elevate blood pressure by negatively affecting the elasticity of the arterial walls. Insulin likewise alters the mechanical action of the blood vessel walls by acting on smooth muscle cells, which stimulate them and make them enlarged. As smooth muscle cells grow, they make the arterial walls thicker and less supple. This forces the heart to work harder and exert more pressure to force the blood through the narrowed vessels.

In women with PCOS, the ovarian follicles start to mature but fail to ripen or to be released. They stay in the ovaries and continue to produce estrogen, but no progesterone. This increases the risk of developing

infertility. Also elevated levels of LH and estrogen have been found in some women with PCOS.[83] This may block ovulation. Likewise, high levels of testosterone inhibit ovulation.[84] Moreover, women with PCOS may miscarry at a higher rate than women without the condition.[85,86] In addition, insulin itself plays a role in ovulation. The ovaries have insulin receptors. Insulin stimulates an increase in LH and androgen levels, decreasing SHBG. In the presence of elevated androgen, LH levels increase and lead to poor follicle development and failure to ovulate.

Importantly, women with PCOS have an increased risk of developing hormone-related cancers. For example, women with a history of PCOS and irregular periods have a 5-fold increase in the risk of developing endometrial cancer.[87] Likewise, one study showed that women with PCOS may have an increased risk of developing ovarian cancer.[88] In addition, women with this endocrine disorder may be at risk for the development of breast cancer, since they tend to be overweight and have hormonal changes that can lead to unopposed estrogen in the body.[89]

Lastly, studies have shown that women with PCOS store fat better and burn calories more slowly than women who do not have PCOS, so they have an increased risk of being overweight or obese.[90–92] Therefore, there are several disease processes that women with PCOS are at risk of developing.

There are many treatments for PCOS. Medications such as antiandrogen, testosterone metabolism blockers, oral hypoglycemic agents, gonadotropin-releasing hormone antagonists, 5-alpha reductase inhibitors, hair metabolism inhibitors, ovulation inducers, and oral contraceptives are used commonly. Surgery is also suggested in some cases.[93–101]

From a metabolic/anti-aging/functional medicine perspective, there is also a lot to offer. Natural progesterone has been found to be very helpful. It is imperative to measure hormone levels before beginning therapy.

Also, there is no disease process that cannot be made better by eating a healthful diet. Studies have shown that high-fiber, low-glycemic-index eating programs, weight loss, and exercise are very beneficial for women with PCOS. To be specific, high-fiber diets lower blood sugar, blood pressure, and cholesterol.[102–104] Furthermore, in a 6-month trial, 18 women with PCOS were placed on a low-glycemic-index eating program along with moderate exercise. The study found an 11% reduction in central fat, 71% improvement in insulin sensitivity index, 33% decrease in fasting insulin levels, and 39% decrease in LH levels; and 50% of the women started ovulating.[105] Another medical trial showed that in women with PCOS, weight loss alone helped 60% of them get pregnant without other medical intervention.[106]

In addition, weight loss alone has been shown to improve the following[107–114]:

- signs of hyperandrogenism
- menstrual irregularity
- hyperinsulinemia
- restoring ovulation and fertility
- improve gonadotropin pulsatile secretion
- may prevent non-insulin-dependent diabetes and heart disease
- decrease ovarian P450c17 alpha activity

Furthermore, when it comes to exercise, several studies showed that women with PCOS who exercised improved ovulation, reduced insulin resistance, and promoted weight loss.[115] Interestingly, one medical trial compared the effects of exercise versus a low-calorie diet in women with PCOS. The women who exercised had a higher ovulatory rate, better insulin sensitivity, and a larger reduction in waist circumference than women who did not exercise.[116]

Reducing stress has been found to be very beneficial for patients with PCOS. Cortisol stimulates the release of glucose, fats, and amino acids for the production of energy in the body. During times of stress, cortisol and insulin levels rise in the body. Cholesterol levels may rise as well. If cortisol is elevated, it decreases the making of progesterone and its activity. Cortisol competes with progesterone for common receptors. Consequently, if cortisol levels are elevated, the symptoms of PCOS can be exacerbated.[117]

Essential fatty acids supplementation may be helpful. They slow down the absorption of carbohydrates in the blood stream. They also decrease inflammation. PCOS has been shown to have an inflammatory component.[118]

Drinking enough water is also very important. It has been estimated that the amount of water that the patient needs to drink daily is one-half her body weight in ounces, if she has normal renal and heart function. Furthermore, a study showed that people who drink 5 to 8 glasses of water a day have fewer heart attacks. Dehydration increases the tendency for the blood to clot.[119]

Being nutritionally sound also helps with the symptoms as well as aiding in the prevention of other disease processes that are associated with PCOS. Vitamin D deficiency is common in women with PCOS. A medical trial found that supplementation with 1500 mg of calcium a day along with 50,000 IU of vitamin D2 on a weekly basis normalized menstrual cycles and/or fertility in all women studied with PCOS-related menstrual irregularities within 3 months of treatment.[120] This was a small medical trial but certainly suggests that more research needs to be done in this area, particularly using D3 as the form of vitamin D supplemented.

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D-*chiro*-inositol is a stereoisomer of inositol. A placebo-controlled trial with 44 women was done where one-half of the women received D-*chiro*-inositol for 6 to 8 weeks versus controls.[121] Insulin and testosterone levels were lowered in all of the women, and 18 who received D-*chiro*-inositol ovulated. Furthermore, evidence suggests that the insulin resistance seen in women with PCOS may be partially due to a deficiency of D-*chiro*-inositol containing phosphoglycan or a defect in its tissue availability or utilization.[122] This nutrient is currently not available in every country. D-pinitol (3-0-methyl-D-*chiro*-inositol) has similar chemical structure and biochemical actions as D-*chiro*-inositol and is available in most countries. D-*chiro*-inositol is also found in high concentrations in buckwheat. D-pinitol is found in legumes, citrus fruits, and soy meal.[123,124] Caution may be advisable in patients with bipolar disorder; some practitioners have expressed concern that a high consumption of inositol may exacerbate it.[125]

Short-term use of N-acetylcysteine (NAC) may be helpful as well for PCOS. Studies have shown that using NAC in conjunction with clomiphene citrate increased ovulation, and pregnancy rates in women with infertility who had PCOS and could not conceive with the use of clomiphene citrate alone.[126,127]

Herbal therapies for PCOS have medical trials that support their use such as adaptogens for stress or herbal therapies to aid in hormonal regulation.

Adaptogens have been shown to improve the stress response and HPA function such as American ginseng, ashwagandha, eleuthero, rhaporticum, rhodiola, and schizandra.[128] Of course, stress-reduction techniques are also important to help to normalize cortisol.

Some herbal therapies affect hormonal function such as *Cimicifuga racemosa* (black cohosh), which binds to estrogen receptors and lowers LH.[129,130] *Vitex agnus-castus* (chasteberry) has several therapeutic effects. It reduces prolactin secretion, since it has dopamine-agonist activity at the hypothalamic-pituitary level, and it also lowers the estrogen-progesterone ratio. Chasteberry also indirectly increases progesterone levels.[131–133] In addition, *Serenoa repens* (saw palmetto) inhibits 5-alpha reductase, which inhibits the conversion of testosterone to dihydrotestosterone (DHT). It also reduces androgen effects at the hair follicle and the pilosebaceous unit, which decreases hirsutism and acne.[134–136] *Urtica dioica* (nettle) root binds to and increases SHBG, which then decreases the amount of testosterone available for the body to use. Nettle leaf does not work for this purpose.[137–139] *Camellia sinensis* (green tea) increases SHBG, which decreases testosterone;and it also has been shown to help promote weight loss.[140,141] A placebo-controlled trial of women with PCOS revealed that the body weight of the group who used green tea decreased by 2.4%, whereas the weight and BMI of the control group was higher at the end of the study.[142] *Glycyrrhiza glabra* (licorice root) can decrease testosterone synthesis, according to research and a medical study.[143–145] Spearmint tea, as with several of the other herbal therapies, has been shown to lower testosterone levels. It also may raise FSH and LH and can improve hirsutism.[146] Maitake mushroom extract (*Grifola frondosa*) in a medical trial was given to patients with PCOS versus clomiphene. After three cycles, the rate of ovulation in the maitake group was 76.9% and the rate of ovulation in the clomiphene group was 93.5%.[147,148] White peony (*Paeonia lateriflora*) has several effects upon hormonal regulation. It increases progesterone, reduces testosterone, and modulates estrogen and prolactin. It also affects the ovarian follicle by its action on aromatase. It has been used in the treatment of PCOS and also for hyperprolactinemia, endometriosis, and ovarian failure.[149,150] Combination therapies are also efficacious. The traditional Chinese formula Shakuyaku-kanzo-to, or TJ-68, a decoction of *Glycyrrhiza glabra* and *Paeonia lateriflora*, has clinical trials showing that it is a very effective treatment for PCOS.[151]

Other treatments shown to be effective for PCOS include detoxification, acupuncture, and weight-loss surgery. Acupuncture can have a positive effect on PCOS patients, since it influences the sympathetic nervous system, endocrine system, and neuroendocrine system.[152,153] A study on women with PCOS who had bariatric surgery showed resolution of menstrual irregularity in 100% of the patients, improvement in hirsutism in 75% of the patients, resolution of type 2 diabetes and ability to stop drugs for hypertension in 78%, and the ability to stop medication for hyperlipidemia in 92% of the patients.[154]

Medicine has changed a great deal in the last 20 years. Through a metabolic/anti-aging/functional medicine approach, we can now look at the cause of the patient's problem and not just treat the symptoms. Likewise, we can customize and individualize the treatment program. This provides patients the best of both worlds, where for disease processes such as PCOS they can have the advantage of conventional approaches along with metabolic medicine therapies.

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Inositol for PCOS

by Megan Chmelik and Jacob Schor, ND

Research on the benefits of potential new therapies, particularly therapies that interest us as naturopathic doctors, rarely advances in a straight line. While one study looks good, the next study doesn't. Sometimes we can blame this on study size and magnitude of change; the number of participants is too few and the amount of change brought on by the intervention is too small and together this prevents statistical significance. Yet sometimes even big studies in which we think things are pretty well proven take a turn. The recent Holmes aspirin for breast cancer paper comes to mind.

In 2010 Michelle Holmes et al. reported in the *Journal of Clinical Oncology* that regular aspirin use reduced the risk of breast cancer recurrence. Using observational data from 4164 women diagnosed with breast cancer who were part of the Nurses' Health Study, they reported that taking aspirin 2 to 5 times per week was associated with a 71% decrease in risk of recurrence (RR: 0.29: 95% CI, 0.16 to 0.52).[1] These are clinically significant numbers, and while many of our patients were reluctant to use aspirin, we have been obligated to encourage breast cancer patients to do so.

In a second and quite similar study, Holmes reported in June 2014 that in a cohort of 27,426 Swedish women there was no association between aspirin use and BC recurrence.[2] Many of us are accustomed to research going back and forth, first it's good, now it's bad; this is how science usually works.

With this in mind, we noticed and want to tell you about something that seems to be an exception to the typical faltering pattern, an idea that so far has advanced in a straight line. As we have watched the growing body of research on the use of inositol for treating polycystic ovarian syndrome (PCOS), it seems to be moving forward steadily. The evidence supporting use of inositol in PCOS just gets better and better with each new publication.

Inositol was first isolated and identified by Johanes Joseph Scherer, who isolated it from muscle tissue in 1850. The name itself comes from a Greek word that means "sinew sugar." In the body, inositol is found as a component of phospholipids. In 1903, Theodor Hartig reported that phytates were high in inositol, and the terms *phytic acid* and *inositol* are still sometimes interchanged.[3] We sometimes worry about foods high in phytic acids, as these compounds block mineral absorption, in particular iron. Interestingly, phytic acids increase insulin sensitivity.[4] Up until the mid part of the last century, it was believed that inositol was a vitamin. Though this has been disproved, we often find it mentioned or listed in association with B vitamins.

Two stereoisomers of inositol found in the body are important in this discussion. The first, myo-inositol (MI), was identified in 1914 by Anderson. MI regulates both follicule stimulating hormone (FSH) and thyroid stimulating hormone (TSH). It also contributes to regulation of glucose uptake. MI may be converted into a second stereoisomer called D-*chiro*-inositol (DCI) by an insulin-dependent enzyme. DCI regulates glucose uptake and glycogen synthesis.

Larner et al. reported in 1988 that both stereoisomers, MI and DCI, mediate insulin action. Over the next two decades, Larner continued to investigate the role of these two inositol forms in type 2 diabetes (DM-2). People with DM-2 have altered ratios of MI to DCI. Their DCI urine levels are lower than in healthy people, and their MI levels are elevated. Lerner theorized that the fault was in the epimerization process, the conversion of MI to DCI.[5]

The time period when Larner's research was published overlaps the years in which PCOS became clearly defined as a disease.

While some practitioners blame PCOS on modern lifestyle, diet, and resultant obesity and insulin insensitivity, such a view is likely in error. Reports of women with symptoms that sound suspiciously like PCOS are noted throughout medical history.

Hippocrates describes "those women whose menstruation is less than three days or is meager, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant."[6]

Moses Maimonides (1135–1204 AD) noted, "There are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman's nature tends to be transformed to the nature of a man, this does not arise from medications, but is caused by heavy menstrual activity."[7]

PCOS is theorized to have originated in Paleolithic hunter-gatherer communities, a time at which PCOS provided survival advantage. Individuals with the greatest capacity for energy storage necessary to endure episodes of hunger, the "thrifty genotypes," have

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an advantage in societies that lack grocery stores or food stamps. PCOS, because it is a "thrifty genotype," would have enhanced survival during times of food shortage, as insulin resistance would have lowered energy expenditure and been an evolutionary advantage.

While modern PCOS women are able to conceive, though at a lower than normal rate, it is possible that in earlier times when caloric intake was lower and energy expenditures greater, the pregnancy rates of PCOS women may have been significantly higher than at present.[8]

PCOS is characterized by the presence of ovarian cysts, elevated androgen levels, and abnormal ovulatory function. According to the current National Institute of Health (NIH) definition, two of the three criteria must be met in order to make a diagnosis.[9] Key features include obesity, acne, and hirsutism. However, PCOS presents in a variety of ways, so diagnosis is often difficult. While the stereotypical PCOS patient has a high body mass index (BMI), hirsutism, and hyperinsulinemia, this image is not the rule. Only about half of women with PCOS are obese; the other half have a normal body mass; this later group is referred to as "lean" PCOS. The other classic symptom, hyperinsulinemia, may or may not be present.

While the symptom picture of PCOS is ancient, actual criteria for diagnosing PCOS were not established by NIH until 2003. That same year saw the publication of the first of several studies demonstrating the benefit of inositol in the treatment of PCOS.

Gerli et al. reported a positive impact from inositol on ovarian function. In their randomized controlled trial, 136 of 281 women took just 100 mg of inositol twice a day. Within weeks of the start of treatment, the group receiving inositol experienced rapid follicular maturation as well as a significant reduction in weight compared with the placebo group, who gained weight.[10] A 2007 study by Papaleo et al. described the effect of MI combined with folic acid. Twenty-five infertile PCOS women took 2 grams of MI per day combined with folate. After 6 months of treatment, 22 of the participants experienced restoration of one cycle with 18 maintaining their results at the time of follow-up. Additionally, nine pregnancies resulted.[11] In a second study by Gerli's team, also published in 2007, 92 PCOS patients were randomized and 45 women received 4 g/day of MI plus 400 mcg of folic acid; the remainder received just folic acid and a placebo. The treatment group had a significantly higher ovulation frequency rate (25%) compared with the placebo (15%), and the time to first ovulation was significantly shorter: 24.5 days compared with 40.5 days.[12] Constantino's 2009 trial reported that women receiving MI plus folic acid combination had other improvements beyond ovulatory function. Women in the treatment group experienced significant decreases in serum total testosterone, serum free testosterone, plasma triglycerides, systolic and diastolic blood pressure, and circulating insulin levels.[13]

Raffone et al. reported in 2010 the results of a trial in which 42 women with PCOS were randomized in a double-blind fashion to receive either 1500 mg of metformin/day or 4 grams of myo-inositol in combination with 400 mcg of folic acid. Spontaneous ovulation was achieved in 65% of the patients receiving MI, with 30% obtaining pregnancy. In comparison, of the women receiving metformin, only 50% ovulated spontaneously, resulting in 18.3% becoming pregnant.[14] Le Donne et al. reported in 2012 results from a comparison of diet alone, diet combined with metformin, or diet plus metformin and MI. Weight loss was linked to use of metformin, while menstrual cycle regulation was primarily dependent on the use of MI.[15] These findings suggest that both MI and metformin are helpful in restoring normal ovulatory function, and that MI may be slightly more effective than metformin.

In just the past 2 years, several important clinical trials have been published that help us better understand the benefits of inositol for patients with PCOS, including several studies that highlight the different roles of myo-inositol and d-*chiro*-inositol.

Colazingari's December 2013 paper reported outcomes of 100 women undergoing in vitro fertilization who received either a combined MI + DCI supplement (1.1 g MI and 27.6 mg DCI) or just DCI (500 mg) daily. Primary outcomes measured included quantity of mature oocytes, FSH levels, and number of grade 1 embryos. Upon completion of treatment, the women taking the MI-DCI combination produced fewer degenerated oocytes, and had a greater amount of mature oocytes and therefore a higher embryo quality as well as fertilization rate.[16]

Pizzo in a March 2014 study reported on 50 women with PCOS, who were treated with either 4 grams of MI plus 400 mcg of folic acid or 1 gram of DCI plus 400 mcg of folic acid each day for 6 months.

"Both the forms of inositol were effective in improving ovarian function and metabolism in patients with PCOS, although myo-inositol showed the most marked effect on the metabolic profile, whereas D-chiro-inositol reduced hyperandrogenism better."[17]

Studies suggest that despite type (lean, obese, insulin resistant, or non-insulin resistant), incorporation of MI into a treatment plan for PCOS is beneficial. In a study involving 42 overweight women with BMIs greater than 25.5, improvements due to MI (2 g/day) and folic acid (200 mcg/d) were found to be more significant in the group that had baseline fasting insulin levels greater than 12 μU/mL; however, the women who had insulin levels less than 12 μU/mL still benefited in endocrine parameters and insulin sensitivity.[18] On the other hand, 24 women of normal weight

and no presence of hyperinsulinemia received a combination of MI (1500 mg), lactoferrin (100 mg), and bromelain (20 mg) 2 times per day, and after 12 weeks of treatment hormonal parameters improved; however, there was no change in BMI.[19]

As can be seen, research on PCOS is progressing not just rapidly but steadily; there doesn't seem to be the common phenomenon of a step backward for every few steps forward. With new studies' being published so frequently, it is likely that the information we have just presented will not remain current for long. Of course we worry that, having described this information in the manner we have, negative studies will now come to light. Still, for the time being, things look straightforward.

For now, research suggests that both myo-inositol and D-*chiro*-inositol are therapeutic for individuals with PCOS regardless of type. It's a bit fuzzy whether or how the ratio between isomers should be adjusted depending on symptoms, but we suspect that this will become clearer in the future. It may be that one ratio is more appropriate for women with higher BMIs, as this presentation is associated with more metabolic alterations.[20]

Positive outcomes have been reported with dosing usually ranging from 2 to 4 g per day; however, additional benefit is suggested when various other supplements and modalities are used in combination with the inositol. Specifically, incorporating some amount of folic acid into a treatment plan may lead to better results, particularly in regard to ability to conceive. Both forms of inositol appear to offer benefit, with the MI having more impact on metabolic symptoms (blood sugar) and the DCI on hyperandrogenism (hirsutism and acne). In cases where metformin is used, inositol supplementation, along with diet and exercise, may produce greater results in symptom reduction.

We spend so much of our time trying to make sense of the discrepancies in research findings, it is a pleasant change to feel as if the studies are making sense, or at least moving in a consistent direction.

Notes

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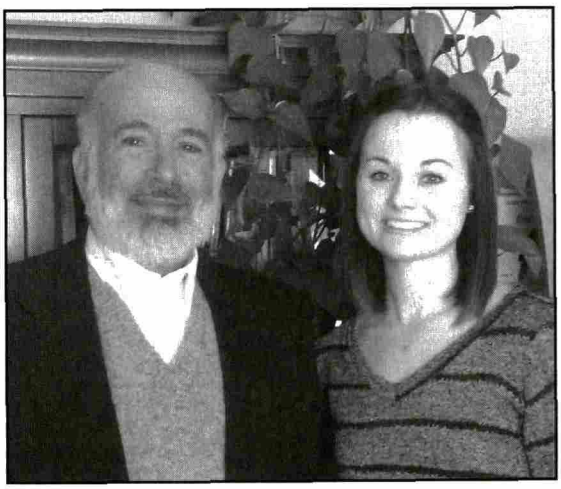

Megan Chmelik, a former dancer with Ballet Arizona, currently lives in Denver, Colorado, and works for Jacob Schor, ND. She will graduate in May 2015 from Metro State University with a major in integrative health care and then this summer move to Portland, Oregon, where she will start at National College of Natural Medicine, pursuing her doctorate in naturopathic medicine.

Dr. Schor graduated from NCNM in 1991 and has practiced in Denver, Colorado, ever since. He is a past president of the Colorado Association of Naturopathic Physicians. He has served on the Oncology Association of Naturopathic Physicians' board since 2008, as secretary, vice president, president and current "past president." He is an associate editor of the *Natural Medicine Journal* and a contributing writer to *Naturopathy Digest, NDNR,* the *Townsend Letter,* and other publications for the profession. He has served on the board of directors of the AANP and is a past chair of the AANP speaker selection committee. Dr. Schor, as a member of the AANP House of Delegates, was instrumental in passing the AANP's current Code of Ethics.

Dialogue: Nutrigenomics and Personalized Medicine

Kristi Hughes, ND, and Yael Shapiro, PhD, RD

Based on an interview with Nancy Faass, MSW, MPH

Dr. Hughes: The new genomic testing ushers in the ability to create a more specific, individualized approach to meet our patient's true needs. These tests give us the capacity to discover unidentified genetic influences that put the patient at potential risk. Frequently there are predispositions that may not manifest for decades. Genetic testing allows us to intervene with diet and lifestyle and make choices at a reasonable point in time that can influence and transition that patient toward a greater state of health. This reduces the likelihood that we will have to work our way backwards from coronary risk, from diabetes, dyslipidaemia, and hypertension. Rather than having to intercede at a later stage in the disease process, these tests enhance our ability to foresee where things could go wrong. At that point, we have the insight to intervene with more appropriate diet, lifestyle, and environmental factors, matched to that specific individual's genomic potential. We are at the beginning of the clinical application of this science, but this approach takes the reality of personalized medicine and personalized nutrition to the next level.

PCR DNA Nutrigenomic Testing

Dr. Hughes: Dr. Shapiro holds a doctorate in nutrigenomics from Cape Town University in South Africa. Tell us about the uniqueness of the test panels you have developed and why they are so clinically relevant.

Dr. Shapiro: DNAlysis is my company and we designed and built the test panels here in South Africa. We have a partnership with Nordic Laboratories, a Danish company in Copenhagen that helps us distribute the tests around the world, in Europe, the United States, and India. The tests originate from us, and we only work with practitioners.

At DNAlysis all of our testing is focused within the field of nutrigenomics. Everything we do is about clinical relevance and utility to support effective clinical practice. When we are deciding what kind of test to develop and which genes to include in a particular panel, we apply a strict set of criteria to evaluate whether a genetic polymorphism is clinically meaningful.

Optimizing Genetic Expression

Dr. Shapiro: In selecting the genes that are included on a particular panel, first we need to know whether a particular genetic polymorphism has an impact on some form of metabolic function. Obviously, there has to be good science to confirm this genetic activity, so we ask for at least three validated studies.

We select for genetic influences that cause changes we can measure in response to clinical interventions, changes that will guide treatment. Testing is used to answer questions such as:

- What is interacting with that gene that is changing our phenotype in some way?
- What type of environmental input will alter the course of this metabolic disturbance?
- Which nutrient(s) will alter the expression of a particular gene?

The point is that every gene and polymorphism included on the test must be clinically useful – there must be a lifestyle intervention that we can recommend, based on the presence of the gene and the associated research literature.

Exclusions

Dr. Shapiro: The BRCA gene is an example of a SNP (a single nucleotide polymorphism) that is impacted very little by diet or environmental factors. External influences on the expression of this gene are exceptionally low – almost negligible. BRCA is a single-gene mutation; by simply having that polymorphism, a woman's chances of developing cancer are as high as 80% to 90%. Although only 5% of breast cancers will be accounted for by the BRCA gene, unfortunately the gene has very little responsiveness to what we can do environmentally. Women who carry the BRCA gene usually have an early onset of breast cancer. Consequently, we do not test for BRCA.

The majority of cancers are quite different. They are the result of a number of different polymorphisms that are influenced by diet and lifestyle, affecting inflammation, oxidative stress, methylation, and detoxification – usually reflecting altered enzymatic or metabolic activity that is interacting with diet or the environment. These cancers develop over decades in response to complex genetic influences rather than as the result of a single gene.

Genetic Panels

Dr. Hughes: What I like about these panels is the selection. In the first test panel, key risk factors are brought together in an overall health profile. The second test is focused on weight management and obesity trends, developed for patients struggling with weight loss. The third test evaluates estrogen metabolism and risk factors associated with detoxification functions. Their fourth test looks at genetic aspects of fitness with an emphasis I haven't seen anywhere else. This profile helps us understand the patient's genetic susceptibility to injury, their recovery processes, and optimal types of exercise for that individual.

Test 1: Health Factors

Dr. Shapiro: Our primary health panel takes a broad look at metabolic health, focusing on factors such as inflammation, oxidative stress, insulin metabolism, and bone health. A SNP in any of the 28 genes analyzed on the test can result in impaired metabolism and eventually in disease. Since these genes influence underlying metabolic factors, rather than causing frank disease, in the past it took extensive testing to fine-tune treatment. For patients with these issues, the DNA Health panel can take some of the guess work out of diagnosis.

We know from the CDC that over 100 million people in the U.S. have some type of chronic health condition, and almost 80 million struggle with obesity. This DNA Health genetic panel is an excellent screening tool for patients with the symptoms of, or full expression of, chronic diseases of lifestyle. All the genetic variants selected for the DNA Health Report can be influenced by lifestyle factors, which means that all can be addressed through proactive interventions.

This panel is also relevant for patients concerned with risks associated with a family history of cardiovascular disease, stroke, diabetes or cancer. In addition, the test meets the needs of patients interested in peak performance – those who want ideal health and body composition. This is the perfect way to learn how optimally a patient's metabolic processes are functioning, the best possible diet, and the best supplements, with implications for issues such as lactose intolerance and caffeine tolerance. In sum, you can use this test to support peak performance, reduce risk, or manage chronic illness.

Test 1:

Lipid Metabolism
- Lipoprotein lipase metabolism
- HDL uptake and CAD risk
- Triglyceride catabolism
- Lipoprotein metabolism

B Vitamins/Methylation
- MTHFR variants
- Homocysteine metabolism
- Hormone and catecholamine levels
- Homocysteine and methylcobalamine levels
- Homocysteine and folate levels

Detoxification
- Glutathione in Phase II detoxification
- Oxidative stress and carcinogen catabolism
- Conjugation of reduced glutathione
- Phase 1 cytochrome P450 metabolism of estrogens and carcinogens

Inflammation
- Low-grade chronic inflammation, correlated with elevated levels of IL-6 and CRP
- Elevated TNF-α associated with insulin-resistance and obesity

Oxidative Stress
- Nitric oxide functions, vascular tone, and platelet aggregation
- Mitochondrial superoxide dismutase antioxidant activity
- Extracellular superoxide dismutase vascular activity

Bone Health
- Vitamin D activity affecting calcium absorption, calcium homeostasis, and bone cell growth
- Collagen a1 and a2 formation

Insulin Sensitivity
- Glucose and lipid metabolism and adipogenesis
- Blood glucose homeostasis, insulin secretion and resistance, increased risk of type II diabetes
- Function of the hypothalamus, vital organs, and adipose tissue, and effects on satiety and energy intake

Iron Overload
- Hereditary hemochromatosis

Test 2: Obesity and Weight Management

Dr. Shapiro. A large portion of the population battles to lose weight. Research from the science of nutrigenomics has found that at a minimum, genetics can account for 50% of obesity and can be an influencing factor as high as 80% in a given individual. In short, genetics is a far more powerful factor in weight management than anyone has acknowledged.

When I was studying dietetics, there was no acknowledgement of genetics. Everything was about diet and lifestyle. Genetics has turned out to be the missing link. Given what we know now, we've come to realize that we will never be effective in weight management until we understand how genetics interacts with weight.

In the past, when we thought about genetics and weight, we thought primarily in terms of factors like metabolic

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rate (some patients seem to gain weight just by looking at food – others can eat as much as they want and never gain weight). In reality there are actually *many* factors that work together to impact weight, establishing individual risk and susceptibility to obesity: for example, the efficiency of fat absorption in the gut, with a resultant level of fats and calories coming into the system.

Genetic resistance to weight loss is common. People do not all lose weight in the same way, nor do they gain weight in the same way, and the speed at which someone gains or loses weight is also influenced by genetics. It is important for the individual patient to understand where they are on the weight loss spectrum, what is realistic weight loss, and how *they* can best optimize their weight loss management.

Genetics also determine how efficient each of us is at metabolizing carbohydrates and fats, how rapidly we burn calories and fats, and how we respond to exercise. What about cravings, sweets, and snacks? Is low carb the best diet or low fat?

Another aspect of working with obesity is to understand clearly how our patients experience hunger, appetite, and satiety, because that is often genetically driven. Some patients do not experience normal satiety. They are not being irresponsible or lacking willpower – they are hungry. Similarly, taste preferences and food cravings are individual and can have a genetic basis.

Dr. Hughes: In my training, we were taught to think of food cravings as the way we respond to blood sugar – insulin levels, metabolism, and blood sugar fluctuations that can set us up for cravings. But you described genes that have an impact on the way we experience the taste of sweetness and whether we crave sugar.

Dr. Shapiro: Insulin is only one part of an individual's blood glucose management. Actually, there is an entire group of genes that give us information about how people respond to sweet foods and we discovered that there is a huge variability in how these genes are expressed. Traditionally, we believed that taste was localized to our tongue, through sensors for sweet, salty, bitter, or spicy. What we've discovered today is that glucose sensors are located throughout our bodies, in our gut, our pancreas, and the hypothalamus. Taste is not isolated to our tongue. So the question of why one individual craves sweets more than another turns out to be much more complicated than just blood sugar management. Successful weight management includes understanding the source of cravings and determining whether genetics is driving those cravings.

The DNAlysis Diet Panel is an excellent tool for answering those questions, given the focus on key metabolic factors: obesity risk; absorption and metabolism, including carbohydrate metabolism; fat metabolism and storage; obesity and satiety; regulation of metabolism and food consumption; insulin sensitivity and regulation of energy intake; inflammation; circadian rhythms; and exercise responsiveness.

Test 3: Estrogen Metabolism

Dr. Hughes: Many women come to my office to discuss the use of bio-identical hormones as an approach to anti-aging. This topic is very complex and includes assessing family history, the current state of the patient's health, and looking at potential risks. How can genetic assessment of estrogen metabolism and detoxification pathways inform those clinical decisions?

Dr. Shapiro: I believe women should have a DNA Estrogen test before they make decisions regarding hormone supplementation or contraception. Estrogen hormones affect the growth, differentiation, and function of a number of target tissues. Improving estrogen metabolism is of benefit to women who suffer from estrogen-dominant conditions such as endometriosis, premenstrual syndrome, and uterine fibroid tumors, or where there is a family history of breast, uterine, or ovarian cancer.

The importance of both estrogen and progesterone in breast cancer development is well established. However, there is a great deal of variability from one woman to the next in the metabolism of steroid hormones and carcinogens, and in phase I and phase II detoxification. Variations in the genes involved in these processes help identify a sub-population of women with higher lifetime exposure to estrogens, estrogen metabolites, and other carcinogens. Understanding an individual's genetic risk factors makes it possible to target our clinical interventions.

The DNA Estrogen Metabolism and Detoxification test includes 10 genes involved in estrogen biosynthesis, estrogen metabolism, and phase I and phase II detoxification. The results provide unique information to guide personalized diet, lifestyle, hormones, and supplement recommendations.

Test 4: Fitness Profile

Dr. Hughes: This profile reveals the types of exercise that are going to be most effective for a given individual, based on genetic predisposition, as well as insight into the recovery process. The test expands our ability to tap into our patients' athletic capacity, to provide guidance for people in their training programs, and to customize nutrition for improved recovery... We haven't seen that anywhere.

Case in point: this test provided me with key insight into challenges my 10-year-old daughter was having in her sport, gymnastics. We all know that gymnastics can be hard on the

young developing body, but when I got back my daughter's report I realized that the emphasis of her nutrition and supplement plan to address her intermittent joint pain was focused in the wrong area. I had been providing her with anti-inflammatory support when my direction should have been towards more optimal mitochondrial function with an emphasis on key antioxidants. Making some adjustments to her nutrition plan was helpful for both her training and overall sense of health.

Ms. Faass: That's amazing! So the test shows how to support optimum performance.

Dr. Shapiro: On the DNA Sport Report, we look at three different areas. One is an individual's potential in terms of performing endurance-type exercise (such as distance running or cycling) compared with power-type exercise (like weight training). Some people have the ability to do both. However, there are others who excel in an endurance environment, but if they emphasize weight training, that can actually be quite ineffective.

We also look at injury potential, which can be a huge issue. Some individuals seem to constantly suffer injury, particularly associated with collagen tissue, such as the Achilles' tendon, the ACL, or the rotator cuff. There are genetic susceptibilities to those injuries that we can look for in the genes, based on strong research literature confirming those susceptibilities. This aspect of the test will help patients reduce their risk of injury, by emphasizing the best sports and even the best position to play to maximize health.

Another important aspect of exercise is recovery, with an emphasis on the differences in how people recover from training. Some people recover extremely well and can get back on the road the next day, and others need greater recovery time. These individual tendencies all have a genetic basis.

We've been working with fitness clients on two levels. Elite sports teams such as rugby teams or cycling teams in Europe are utilizing the tests primarily to minimize injury and maximize recovery. We also work with recreational athletes who just want to make their training time count – people who are already running or training and want to take that to the next level. They want to make sure they are using the limited amount of time they have to work out in a manner that is genetically compatible. These tests are very empowering for both the practitioner and the patient.

Benefits of Genetic Testing

Researching Test Impact

Ms. Faass: Excellent. Do you have outcomes data on patients who have made lifestyle changes based on their test results?

Dr. Shapiro: That's a question that we've discussed in great detail. One of the limitations in evaluating the impact of nutrigenomics testing is that nutrition and lifestyle interventions involve so many factors, it is extremely difficult to tease out the influence of genetic information on patient outcomes. Rather, we prefer to view access to genetic information as another good tool in a practitioner's toolbox. We give providers an additional layer of information, so they can evaluate health at an individual metabolic level, identify imbalance, and focus their interventions on fundamental health issues based on individual genetic predispositions. This provides a real clinical advantage to the practitioner. However, once the practitioner decides which intervention plan to put into practice, there are a tremendous number of factors that could influence whether that patient is going to make those behavior changes.

We cannot measure the impact of our genetic tests because they are part of a much bigger picture. This research is not comparable to that done on the BRCA gene, which tracks outcomes associated with a single gene and one intervention (whether or not to have a mastectomy). Nutrition and exercise recommendations are part of an entire treatment plan, and we are only one aspect of the intervention. We do not supersede other information that the practitioner has – we only add another level of information that they did not have access to previously.

Lifetime Relevance and Patient Compliance

Dr. Shapiro: These are tests that are only done once. This is information that does not change over a lifetime. Whatever they learn in their report will be relevant to their health for the rest of their lives.

What we do know is that using genetics in clinical practice changes behavior and compliance. This is a decided advantage, given the world we live in, where we have so many nutritional choices. We are all confused about issues like diet and weight loss – in fact, most people are totally overwhelmed. We have found that patients can be very motivated by the idea that this *their* information, unique to them. There is a kind of a personal responsibility associated with that information. The research has found that nutrigenomics testing enhances behavior modification and motivation for change. Particularly with nutrition, that motivation is a huge part of the work.

A Systems Biology Context

Dr. Hughes: What I really appreciate about the approach Yael's team is taking is that they work within a systems biology, functional medicine framework. Their clinical feedback and their test reporting offer clinically relevant

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insight on how genetics can participate as underlying causes of disease. In functional medicine we call those factors antecedents. DNAlysis is doing a very nice job helping practitioners uncover antecedents and predisposing factors their patients may have. The tests provide genetic information in the context of specific functional disorders such as chronic inflammation – as well as health conditions – using a systems biology philosophy.

Triaging Clinical Interventions

Ms. Faass: And do the test results also focus the effort and recommendations of the clinician and narrow the amount of information that they have to deal with?

Dr. Hughes: I would say very much so. That's one of the reasons we will be working with this new testing moving forward: it opens up the awareness of where you may want to go next in terms of further appropriate testing. I think it truly allows us to make better clinical choices about additional assessments without running too many tests or choosing to run the wrong tests when we have nothing to go on but suspicion or intuition.

Dr. Shapiro: The genetics allow you to see which of the metabolic areas need the greatest attention. When patients experience severe chronic illness, their presentation can be quite confusing, so we use the genetics to isolate the underlying dynamics. We recommend looking for the three metabolic areas that are the most compromised, three nutritional areas that need the greatest modification, and three supplements that would be the most effective. This helps to flag important issues, enabling practitioners to triage the interventions, and supports very specific, practical recommendations. From there practitioners can decide whether they need to do more functional laboratory tests, or whether they have to do a different kind of assessment. It gives them somewhere to start, based on specific genetic information at a metabolic level that identifies the processes that are not functioning optimally.

Clinical Support

Dr. Shapiro: We don't expect the practitioner to see the genetic results and be able to work out for themselves the implications of the results; we do all the interpretation for them. We look at the impact of the genotypes. We look at how powerful particular genes are relative to other genes. The report provides a focused interpretation. Additionally, the data is color coded so the practitioner (and the patient) can see immediately the areas that need the greatest attention.

Dr. Hughes: For quite some time now we've seen the emergence of nutrigenomic testing, but much of it has been driven by patients. Our patients walk in the door with their 23andMe test results and say, "Here! Here is my genetic code. What does it all mean?" And they hand us a page full of numbers, without any reporting that might support a clinical direction. (In all fairness to 23andMe, they are currently precluded by federal policy from providing genetic health interpretations.)

Unfortunately, there is very little effective training available anywhere right now for the general practitioner to understand the scope of nutrigenomics and how that translates into clinical practice and clinical utility. There are experts who are dedicating their careers to this emerging field, but the primary care provider is often the one being asked directly. For quite some time, Genova was a leader in the practitioner field. Then we began to see different types of software companies emerge that would run the raw genetic data and generate a report identifying probabilities or patterns. The challenge is that when this kind of data is provided to patients, it is never put in full context. The concern many practitioners have is around how those programs were created, who determined the clinical correlations, and whether they are reliable. There are many opinions in this field about what to say regarding genomic risks; some practitioners voice the opinion that these reports tend to be overstating or overreaching in their suggestions.

What I really find exciting about the approach DNAlysis is taking is the way they present the information clinically. They look at each SNP as it relates to clinical care. For example, reporting on TNF-α might emphasize risk for increased TNF-α production in association with general inflammation or might flag TNF-α or interleukin expression that is disrupting blood glucose management and accelerating metabolic disease.

What is unique and new about their approach is the way in which they are educating practitioners and physicians, putting the genetic results into context in relation to metabolic processes and applying that information to the physiology of the individual patient so that it translates into a clinical application. They are also leveraging their due diligence in ongoing review of the literature to validate the importance of those SNPs.

The testing includes only SNPs from the clinical research with reproducible interventions. They are not emphasizing rare genes that cause rare diseases. There's no sensationalism around their work – they are not over-reporting or overstating the importance of the data (which is rampant right now, given the unregulated nature of this field online).

Practitioner Training

Dr. Shapiro: There is one more aspect of the DNAlysis program that I feel is extremely important, and that is the practitioner training we provide. Every time I come back

to the United States, the lack of genetic training for health professionals is always striking to me.

Generally speaking it is extremely difficult for providers to access training. The IFM includes nutrigenomics in all their programs, but other than those courses, there isn't really any place that practitioners can go and upskill themselves to the point where they feel comfortable working with these tests. This is true whether they are medical doctors, dieticians, chiropractors, naturopaths, or nutritionists.

At DNAlysis we realized this when we started – if we did not have practitioners who knew what to do with the information, it would be impossible for them to use our testing effectively. It can be more harmful than helpful if a practitioner does not understand what they are working with. So we knew early on that practitioners would need to go through a certain amount of training before they would be allowed to work with our tests. That has been my greatest area of concern and, as a result, the emphasis of my work in the last couple of years.

Ms. Faass: How is the training structured, and how many hours are required – what's involved?

Dr. Shapiro: Originally we ran two-day training workshops. But there have been just two trainers world-wide and obviously we can only travel so much. So my company developed a correspondence training with a book and a CD, but even that has not been enough. So I have been working on developing an online training program for practitioners, focused on nutrigenomics in clinical practice. The course is based in functional medicine and systems biology. This is amazing information, but also highly practical. Our plan is to provide practitioners with this course in mid-2015.

Dr. Hughes: This is incredibly focused, in-depth training, compressed into a 12-week course that was developed with busy practitioners in mind. In addition, I really like their report form, the way it simplifies the information, identifying what is most important and what is truly a risk factor, putting that in the context of the scientific literature. This gives us is the ability to translate the data into a true clinical concern.

For the practitioner, I think there are layers of learning. The first is how to identify the biggest risks and move forward with general dietary and lifestyle modifications. Once you start to get comfortable addressing those risk factors, physicians can start to dive deeper and deeper into the individual meanings of the different SNPs and what to do about them. For me, this will be a lifelong interest and a part of my medical education journey. I am constantly trying to update and refresh my knowledge in this changing field. I believe that Yael's course is going to be the springboard that takes practitioners to the next level of depth and individual competency, to the point where they rely a little bit less on the lab and start to really grasp the content. The training will help guide practitioners in this overwhelming field and improve their ability to frame this information in an effective way with their patients, while providing training to create more sophisticated and personalized approaches. This is truly the next era of personalized intervention.

Dr. Shapiro: We are happy to work with practitioners in the U.S. who have functional and integrative medicine training. Right now we work on a one-on-one basis to some degree. Practitioners who have never encountered nutrigenomics are not allowed to work with our tests until they have had proper training. But anyone who is working in an integrative or functional space has already been exposed to this information. With the new course, we hope to be able to take them to a much more powerful level, so they can use the test data to maximum potential. As Kristi said, the emerging field of clinical genomics is a journey that attracts leading edge practitioners, and we are happy to partner with them, providing the most current testing and information available.

Yael Shapiro, PhD, RD

Yael Shapiro obtained her doctorate in nutrigenomics from the University of Cape Town and specializes in the genetics of obesity. She is co-founder and director of DNAlysis Biotechnology and through her second company, Manuka, is developing an online course for health practitioners, *Capturing The Nutrigenomics Conversation*. A professional trainer, she has worked with thousands of health professionals in South Africa, the US, UK, and Dubai, and her training DVD's are used by health professionals throughout the UK, Europe, Scandinavia, the Middle East, India, and Malaysia. She has developed and taught nutrigenomics courses at the post-graduate level and is also coauthor of a book for consumers on diet and lifestyle, *It's Not Just Your Genes*. Dr. Shapiro has been involved in several research collaborations with academic partners, is currently an adjunct Assistant Professor teaching nutrigenomics at Rutgers University, and is completing an MS in the economics and public policy of food at Marylhurst University in Portland, Oregon.

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DNAlysis
DNAlysis tests are distributed globally by DNALIFE®, a collaboration between Nordic Laboratories and DNAlysis Biotechnology

Test panels will be available in the US beginning June 2015.

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Manuka

Manuka was founded to provide a global platform for the provision of progressive, cutting-edge, and credible nutrition education for health practitioners. In February 2015, Manuka will launch with a one-day training conference in Translational Nutrigenomics, to be followed by the launch of an online Nutrigenomics training course, Capturing the Nutrigenomics Conversation, in June 2015. Anyone interested in the Translational Nutrigenomics conference DVD or the online Nutrigenomics course should contact Yael.

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Kristi Hughes, ND
Dr. Hughes serves as Director of Medical Education for IFM, where her role includes the development and supervision of teaching teams in the Functional Medicine Certification Program and the Path to Functional Nutrition. She is involved in the creation of clinical tools and patient education resources that empower healthy lifestyle change. As a trainer in lifestyle and functional medicine, she has lectured extensively throughout the U.S. and internationally for more than 15 years and has been instrumental in providing functional medicine resources for clinicians and nutrition professionals through her role as the Director of Medical Education at Functional Medicine South Africa. Founder and director of the Dynamic Healing Centers in Minnesota, Dr. Hughes also manages a team of health care providers and naturopathic practitioners. The Dynamic Healing Centers support preceptorships, host a naturopathic residency program, and model the integration of functional medicine with a naturopathic foundation. Through the Centers she provides distance consulting to physicians and to patients in conjunction with their physician's participation, with an emphasis on therapeutics such as supervised detoxification.

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Institute for Functional Medicine Annual International Conference – May 28-30, 2015
JW Marriott, Austin, Texas
The evidence that almost all disease results from the interaction of genes with the environment is now extremely convincing. The emerging science continues to confirm that, in the overwhelming majority of cases, genes don't actually cause disease; rather, they influence a person's susceptibility to disease. It's not nature vs. nurture, but nature *and* nurture. Our genetic heritage (or genotype) is still unchangeable (at least for now), but how those genes behave (our phenotype) is very much affected by the environment in which we bathe them.

The 2015 Annual International Conference will focus on the exploding literature that describes how variations in single nucleotide polymorphisms (SNPs) can, in concert with environmental triggers, change the way we metabolize drugs, affect how we excrete or biotransform toxins, modify how we respond to stress, and control how we assimilate and utilize nutrients. In short, these genetic SNPs, in concert with the environmental milieu, can increase or decrease our risk for a variety of diseases. This reflects our changing understanding of personalized medicine and brings the decoding of our personal DNA fingerprint much closer to reality.

For clinicians, the challenge is how to translate complex, molecular technologies in the laboratory, and a growing body of human research into actionable information that has clinical relevance. We have to be able to explain and apply the science to patients in meaningful ways. The 2015 Annual Conference will delve into the science of individual genomic fingerprints as well as their phenotypic expression and plasticity. It will help clinicians adapt this leading edge of medical science to practical, personalized, clinical applications.

For more information, see www.FunctionalMedicine.org under Upcoming Conferences.

Editorial
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'Hidden' HCG Breakthrough May – for the First Time Ever – Totally Eliminate or Control Excruciating Endometriosis

by Jonathan V. Wright, MD

Reprinted with permission from Dr. Jonathan V. Wright's *Nutrition & Healing*, December 2014.

A new "hidden" use for human chorionic gonadotropin (HCG) has been uncovered. It turns out that hCG – the hormone secreted in the largest quantities by human placentas – may be an effective remedy for painful endometriosis. Fortunately, this research was reported "only" 10 years ago, and hasn't lain buried for 31 years (for that, see the December 2012 and February 2013 of *Nutrition & Healing*, which covered previously buried research about hCG, and the stunning story of the reversal of severe spinal cord damage).

This research was first published in 2004, and since that time no contradictory reports have been published. In other words, there's absolutely no reason why this safe, natural therapy shouldn't already have been tried for the thousands (or more likely tens or even hundreds of thousands) of women who've in effect been told, "There's no treatment for your problem except for birth control pills, pain pills, or surgery, but it'll improve after menopause, so hang in there."

Endometriosis is reported to occur in 6% to 10% of all women. In this condition, cells that line the uterus migrate outside the womb to other areas in the pelvis. There they remain and grow, often causing painful menstrual periods and/or mild to severe chronic pain between menses. Endometriosis is associated with infertility, too.

In this research, 31 women with histologically verified (tissue samples were observed under a microscope to confirm the diagnosis) endometriosis were given 1500 to 5000 IU of hCG once or twice a week for 3 to 12 months.[1] The results?

HCG Significantly Reduced Pain, Irritability, and More

Let's quote the researchers themselves: "Three months of hCG therapy led to a highly significant reduction of endometriosis-related pain ($p < 0.001$) and to improvement of disease related parameters such as sleeplessness ($p < 0.001$), irritability ($p < 0.001$), overall discomfort ($p < 0.001$), depressive moods ($p < 0.001$) and painful defecation ($p = 0.01$). Dyspareunia [painful sex] and dysmenorrhea [painful menses] also clearly improved (both $p < 0.001$), though HCG did not lead to significant reduction of dysuria [painful urination] ($p = 0.66$). Prolonged therapy with hCG for up to 12 months (mean: 4.42 months) did not lead to reduction of the beneficial effect."

That's impressive: Endometriosis pain, sleeplessness, irritability, overall discomfort, depressive mood, and painful bowel movements all significantly improved. The only parameter that didn't greatly improve was painful urination. And the treatment continued to be effective for up to 1 year, when (apparently) the research project ended.

The report summary concluded: "hCG injections lead to significant and clinically relevant reduction in pain intensity and to greatly improved quality of life in women with therapy-refractory endometriosis."

So if you or a loved is suffering from endometriosis and you would rather not take birth control pills, be on a continuous dose of pain pills, have your uterus removed surgically, or wait for menopause – why not consider taking this article to a skilled physician knowledgeable in natural medicine and natural hormone use, and discuss giving regular hCG injections a try?

Of course, even though the results of this research were very positive, results are never guaranteed. But clearly there's reason to hope!

Natural HCG Appears to Be Safe

Unfortunately, we've not been able to find any follow-up research published since this 2004 report. And the group was small, only 31 women. But HCG is safe; we all had exposure to it for approximately 9 months when we were vulnerable fetuses, during which time it did us no harm at all. There's also experimental evidence showing the nontoxic nature of even enormous quantities given to adults.

Some physicians and pharmacists worry about the safety of large quantities of hCG, most likely because the amounts used in "hCG diet plans" have been quite small, 125 to 200 IU daily at most. Of course the safety of any therapy is an important consideration.

To put hCG in perspective, however, we need to remember that ➤

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we all essentially "took a bath" in hCG for the first 9 months (some of us perhaps less) of our lives while we were inside Mom. As tiny as we were, we of course emerged unharmed by the large quantities of hCG that we were exposed to.

Another clue to hCG's safety can be taken from a research study that used relatively enormous quantities of hCG, given intravenously.[2] Researchers gave 100,000 to 150,000 IU of HCG to 8 men as part of a research study on hCG and thyroid function. Among other things, the researchers wrote: "No clinical side effects were noted... after iv administration of these large doses of hCG."

Although it's possible for anyone to react adversely to anything, at present it appears that relatively large quantities of hCG are safe.

Buried Endometriosis Treatment Number Two Is Revealed: Going Gluten-Free Significantly Slashed Endometriosis Pain

Just above, you read about the remarkable, but "buried," 2004 research report about a very successful treatment for endometriosis. It's definitely worth repeating! The researchers reported that 1500 to 5000 IU of HCG treatment once or twice a week for three months "led to a highly significant reduction of endometriosis-related pain ($p < 0.001$) and to improvement of disease related parameters such as sleeplessness ($p < 0.001$), irritability ($p < 0.001$), overall discomfort ($p < 0.001$), depressive moods ($p < 0.001$) and painful defecation ($p = 0.01$). Dyspareunia [painful sex] and dysmenorrhea [painful menses] also clearly improved (both $p < 0.001$), though HCG did not lead to significant reduction of dysuria [painful urination] ($p = 0.66$)."[3]

This is a terrific breakthrough for an excruciatingly painful condition for which there has been no effective treatment! And now there's even more good news about endometriosis relief: it appears to be yet another condition that responds significantly to gluten elimination.

In 2011, Swedish researchers reported that women diagnosed with celiac disease (a major type of gluten intolerance) had an increased risk of endometriosis.[4] Although they didn't report about endometriosis risk in women with "non-celiac gluten intolerance" as well, there's good reason to suspect the same increased risk.

In 2012, Italian researchers published results of a study in which 207 women with chronic pelvic pain caused by endometriosis were placed on a gluten-elimination diet for 12 months.[5] One hundred fifty six (75%) of the women had significant pain relief; 51 (25%) did not. None had worsening of pain. But even though pelvic pain was relieved in "only" 75%, all – 100%! – of the women reported what the researchers termed a "considerable increase" ($p < 0.005$ for the technically inclined) in vitality, social functioning, and mental health.

Since women have been reported to find dramatic relief from endometriosis using HCG, it might seem as if eliminating gluten is unnecessary; but for the best total body health results, anyone with endometriosis should always use HCG *and* go gluten-free. Even if HCG eliminates the pain of endometriosis, the underlying gluten sensitivity, especially if "hidden," will cause many other health problems usually undiagnosable by conventional medicine. In fact, nonceliac ("hidden") gluten sensitivity almost always inhibits the assimilation of multiple nutrients, resulting in a variety of health problems.

Buried Endometriosis Treatment Number Three: Melatonin Significantly Relieves Endometriosis Pain

Now we've just (at the time of this writing) found a research report about relief of endometriosis pain with melatonin, the hormone best known for its sleep-inducing activity. (To read many other details about little-known actions of melatonin, including its ability to improve the insulin secretion in prediabetes 2 and diabetes 2 itself, see *Nutrition & Healing* for October 2010.) This time, it's Brazilian researchers, reporting about 40 women with endometriosis, aged 18 to 45, 20 of whom took placebo, 20 of whom took melatonin (10 mg) for eight weeks. Analysis showed that (compared with placebo) melatonin treatment reduced daily pain scores by 39.80% ($p < 0.01$, for the technically inclined) and pain with menstrual periods ("dysmenorrhea") by 38.01% ($p < 0.01$ again). Melatonin improved sleep quality and reduced painkiller use by 80%.[6]

Just a thought: all of this breakthrough research for women with endometriosis was done in Austria, Sweden, Italy, and now Brazil, not in these United States. None of it was publicized by the American media in 2004, 2011, 2012, 2013, or since. Makes one wonder what other non-patent-medicine remedies for other chronic problems are also being ignored.

Thank you to Tahoma Clinic physician-researcher Ronald Steriti, ND, for finding these "breakthrough" publications, the implementation of which may well relieve intractable pain for tens of thousands of women! And, of course, thanks to the researchers who did the original work, and the women who participated in the research.

Notes

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Letters to the Editor

Elevated Estrogen Is Feared by the Medical Profession; However, the Medical Profession Does Not Measure Total Estrogen

The medical profession is concerned about estrogen causing inflammation, allergies, autoimmunity and cancer; however, the medical profession is *not* measuring total estrogen.

Treating the medical *effects* of diseases in humans and in animals may be vital, but treating the *cause* of many of these diseases is even more important.

The medical profession knows that elevated estrogen will cause inflammation of all the endothelial cells that line the arteries of the body, which can cause oxidative stress and damage free radicals, which may lead to allergies, autoimmunity, and cancer.

This is what I have found as a veterinarian and would like to share; unfortunately, most medical education only teaches testing for estradiol, estrone, and estrin in women, and estradiol in men. In animals, only estradiol is measured, unless the blood sample is sent to a specific veterinary laboratory that tests for total estrogen.

The medical profession has very little recognition of adrenal estrogen produced by the inner layer adrenal cortex; however, there is a medical mention of androgen, which is produced by that same adrenal layer, referred to as the zona reticularis.

In 1948, cortisol was classified by one medical group in its literature as the X-Substance and, when used medically in high doses, caused many side effects. This medical vector has continued to plague the medical profession, even today in many medical practices.

It seems not be understood that a normal human being and animal must produce 30 to 35 ug/dL units daily of an active cortisol, if the organism wants to avoid developing allergies, autoimmunity, and cancer.

Dr. William McK. Jefferies also recognized this fact, as I did in animals in the 1970s. Dr. Jefferies published a book called *The Safe Uses of Cortisol*. I have listed several of my books on www.drplechner.com, under "Books Written by Dr. Plechner," which deal with this same subject, but in animals. However, it does relate to humans as well.

This fear of cortisol and the lack of realization that it takes a certain amount of daily cortisol to interact with the hypothalamic pituitary axis in a negative feedback mechanism is still prevalent in most medical practices for humans and for animals.

The human medical literature is aware of the fact that all kinds of input can reduce proper cortisol production. Stress, improper exercise and nutrition, chemicals, radiation, anesthetics, vaccines, etc. are all thought to reduce cortisol production or cause the cortisol to be produced in a defective state, which the body cannot use or recognize.

The significance of this cortisol imbalance is still not realized!

The medical profession is aware of the fact that natural cortisol, produced by the middle layer adrenal cortex, works with the hypothalamic pituitary axis in a negative feedback mechanism.

After the cortisol has regulated the immune system and fulfilled its other functions in the body, the liver breaks down the cortisol, and the kidneys excrete those broken down products.

This is referred to as negative feedback mechanism.

However, if the natural cortisol production is deficient, bound or defective, funding this negative feedback mechanism will not occur. The hypothalamic pituitary axis will not recognize this imbalance, and the ➤

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pituitary gland will keep releasing ACTH, in hopes of having more natural cortisol also released.

When there is not enough natural cortisol produced in any form in order to fund this negative feedback mechanism to the hypothalamic pituitary axis, the pituitary will continue producing its ACTH.

Since the middle layer adrenal cortex can no longer respond effectively, the inner layer adrenal cortex will respond, with a positive feedback mechanism that produces excess amounts of estrogen and androgen.

For some reason, adrenal estrogen is not included in total estrogen measurements, and this is the reason why the cause of allergies, autoimmunity, and cancer may not have been recognized or discovered.

This a simple test that can be performed with any human laboratory.

Even as a frustrated "plain wrap" veterinarian, I have developed a simple animal and human protocol that can be easily measured with a blood test. Why not check total estrogen, and then decide if there is a need to reduce this hormone which causes unconditional tissue growth when exposed to normal tissue?

The human protocol can be reviewed at www.drplechner.com under "Get Help" and "Test Procedures/Info."

The elevated total estrogen, which includes inner layer adrenal zona reticularis estrogen, is the basis for most inflammatory diseases, including allergies, autoimmunity, and cancer. Unfortunately, total estrogen is rarely tested.

Hopefully this will remind physicians that this elevated, inflammatory estrogen is the basis for Alzheimer's disease and many other autoimmune diseases.

Why not test total estrogen in your patient?

If you patient is still menstruating, check her total estrogen the first week of her menstrual cycle when her ovarian estrogen is the lowest, and again when her ovarian estrogen is the highest, and the difference will be zona reticularis, adrenal estrogen.

Why would an estrogen supplement be prescribed for a postmenopausal woman when her estradiol is decreased but her adrenal estrogen is elevated?

I have been asked to get involved with patients who were postmenopausal and their estradiol levels were decreased.

Their physicians suggested using an estrogen supplement or an estrogen patch.

This would be fine if their total estrogen were 40 pg/ml or lower; however, when their total estrogen was tested, it was much higher than 40 pg/ml, and if an estrogen replacement was prescribed for them, it may cause them to develop all kinds of allergies, autoimmunity, and cancer.

The human medical literature does not realize the fact that when a woman goes through menstruation, and her ovarian estrogen peaks, if her adrenal estrogen is also elevated, she may suffer from migraine headaches and possible epileptic seizures.

In animals, idiopathic estrogen comes from elevated total estrogen.

Men who have decided that their libido needs a boost, or female athletes who decide to take a transdermal or injectable testosterone supplement for better performance, may cause themselves to develop allergies, autoimmunity, and cancer, without realizing this.

The medical literature discusses the fact that fatty and other tissues contain an enzyme called aromatase. The literature also indicates the fact that aromatase can turn female androgen, produced by the inner layer adrenal cortex, into a form of estrogen called estrone.

Aromatase production in males, can turn their testosterone into a form of estrogen called estradiol. The more fat that your body contains, the more estrogen transformation may occur.

For their own medical safety, please, with female patients, first measure their total estrogen, androgens, and estrone; in males, please measure total estrogen, estradiol, and testosterone levels before ever giving any testosterone supplements.

Two weeks after the patient, begins to take the testosterone supplement, please recheck the above-listed hormones, and see if their androgen and testosterone are increased and total estrogen is not. But if the total estrogen is increasing, continuing the testosterone supplements will not help males with their libido nor female athletes with their performance, but may cause them major health problems.

These are only my thoughts as a veterinarian, and I do hope that they help the medical world.

Sincerely,
Dr. Al Plechner

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Whole Foods to Fight Cancer

review by Katherine Duff

The Whole-Food Guide for Breast Cancer Survivors: A Nutritional Approach to Preventing Recurrence
by Edward Bauman, MEd, PhD, and Helayne Waldman, MS, EdD
New Harbinger Publications Inc.; 5674 Shattuck Avenue, Oakland, California 94609
© 2012; softcover; $18.95; 247 pp.

A woman is diagnosed with breast cancer, goes through conventional treatment and has a good result – now what? There will likely be a fear of recurrence, and doing something about it may be the best response. The *Whole-Food Guide for Breast Cancer Survivors*, by Edward Bauman, MEd, PhD, and Helayne Waldman, MS, EDD, offers a plan for diet and lifestyle changes that while not curative, will afford a better chance that there will not be a recurrence.

The authors note that cancer is a chronic disease of the genome. This is not to say that women with the BRCA-1 and BRCA-2 genes will all develop breast cancer, because they will not. Rather, anyone can develop cancer at any time triggered by any one of many possibilities of genetic predisposition and other factors such as diet, hormone levels, environmental exposures, physical activity, and more.

The foundation of their plan calls for minimizing one's risk factors with nutrition and their Eat for Health diet. The diet addresses liver and digestive health, hormone balance, and positive gene expression. While we are likely aware of some of the risk factors for developing breast cancer such as age, weight, lack of exercise, and certain genes, emerging research identifies newly discovered risk factors. Among these are inflammation, high blood glucose, a poorly functioning digestive system, and a weakened immune system. Each of these factors and how they may cross over to other risk factors is discussed in this book.

High blood glucose may be the most problematic of all risk factors. Cancer cells rely on sugar for growth. A diet high in sugars and simple carbohydrates causes high blood glucose levels, but that is not all. Such a diet also promotes the release of insulin and insulin-like growth factor, which are known cellular-growth promoters. Obesity can also be the result of such a poor diet and excess weight is another risk factor for breast cancer.

Fat tissue produces estrogen, which results in higher levels of the hormone in the blood. In addition, the hormone called sex hormone-binding globulin (SHBG) binds to estradiol, which is beneficial; but in obese women the levels of SHBG are lower, which makes more of the hormone available to breast tissue. Also, a diet that contains high-fructose corn syrup was found to reduce circulating SHBG by 80%, which resulted in higher levels of circulating estrogen.

Chronic inflammation, another risk factor for cancer, is also tied to excess blood glucose as well as other factors. Trans fats, oxidative stress, and unrecognized food allergies and sensitivities are known to cause inflammation. In addition to recommending foods that will address these issues, the book offers methods for identifying potential food sensitivities, such as gluten.

The Eat for Health diet is designed to avoid cancer-promoting foods and opt for cancer-preventing foods. Plant foods are described as the first line of defense. The phytonutrients in whole foods provide antioxidant protection and anticancer activity, so the diet is high in fruits and vegetables. Simple carbohydrates should be replaced with complex carbohydrates such as whole grains and root vegetables that will increase blood glucose more slowly. Proteins are best obtained from wild fatty fish; legumes; whole grains; and organic, free-range meats. There are several charts that demonstrate the nutrients in these foods, which research has shown have anticancer activity. For example, wild fatty fish contains omega-3 fatty acids that are anti-inflammatory and downregulate the cancer-promoting PcG gene.

"The Eating for Health approach to improving eating habits and food choices supports health and contributes to protecting healthy cells from becoming cancerous. ..."

The authors refer to the diet as nondogmatic and flexible. It is intended to give the necessary nutrients through food sources as opposed to a regimen of supplements to counteract a poor diet. But nutrient deficiencies may occur that will call for the use of supplements. Certain pharmaceuticals, for example, have been found to deplete nutrients. A chart is included that identifies the drug and the nutrients that may need supplementation. They provide a course in selecting the correct supplements and assuring that the ones purchased are of high quality.

Outside the realm of diet, there is also a discussion of environmental pollutants that contribute to cancer growth. These toxins are found in pesticides, plastics, and personal care products. The link between some pesticides and breast cancer has been known for decades. Some chemicals are known to mimic the hormone estrogen in the body, and bisphenol A, an ingredient in plastics, is thought to be one of those. While this chapter is quite abbreviated in its discussion, the authors do refer the reader to other books and sources for more information.

This book may appear as if it is directed to just the breast cancer survivor, but there are other goals too. The authors are part of a movement they call *integrative oncology*, which they define as the combination of "traditional and contemporary natural health and wellness philosophies in addition to conventional cancer treatment modalities." They wish to expand this philosophy into a network of health professionals who would include nutritional consultants and mental health professionals.

The Whole Food Guide for Breast Cancer Survivors enables us to see the connections to the many risk factors and the role that our nutrition can have in either promoting cancer or inhibiting cancer's growth. So while the target audience is for breast cancer survivors, the supporting research is not limited to just breast cancer tumors. The information here is relevant to preventing tumor growth through nutrition for everyone.

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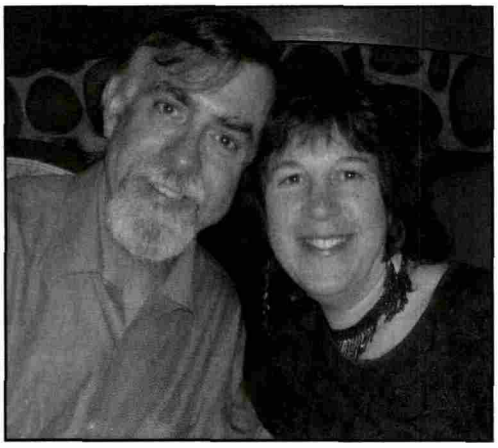

Healing with Homeopathy

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

www.healthyhomeopathy.com

Homeopathy for Climbing a Volcano!

Some material excerpted from *The Savvy Traveler's Guide to Homeopathy and Natural Medicine: How to Stay Healthy Wherever You Go!* (Picnic Point Press; June 2014)

Homeopathic Kit: Heavyweight Natural Medicine in a Lightweight Package!

You may be under the misconception that homeopathy takes a long time to work and is only useful for simple conditions. Neither is true. We want to show you that you can reliably count on homeopathy, the safest medicine that you will ever find, on a volcano climb as much as in the comfort of your own home. First-aid and acute homeopathy remedies act quickly and effectively, and are easy to take with you wherever you go. We want to share our recent personal experience in hopes that you will give homeopathy a try the next time that you, maybe not climb a volcano, but at least take a walk in the woods or the park. It's so much more natural, cheaper, and easier than carrying along over-the-counter or prescription pharmaceuticals.

A Long-Awaited Adventure

We've been looking out our front door, in Pucón, Chile, at Volcán Villarrica for 9 years. We're hikers and backpackers, but climbing the volcano (did we mention active?) seemed daunting. Thinking it a "bucket list" must, or "if not now, when?" we decided to go for it! Friends of ours run climbs through Summit Chile, the safest of the many outfitters here. We got fitted for our rental gear a few days ahead, then waited for the best possible weather conditions. There is up to 1 death per year on this climb (minimal, since there were easily 200 climbers the day of our climb), but we didn't want to be among them! We were given heavy boots (they made the trek more difficult, but since we hiked in snow with crampons all the way up, better to have used theirs than our lighter ones); ice axe; and heavy, hooded jackets, ski pants, gloves, gaiters, helmets,

Volcán Villarrica exploded on March 3, 2015, causing the authors to evacuate their home in Pucon.

and packs. And a butt-sized plastic slider to save for the descent. It was the opposite of our ultralight backpacking equipment, for sure. Backpacking near Mount Rainier a year ago, we ran into a couple of young men who were hiking the Pacific Crest Trail from Canada to Mexico and picked their brains a bit about their packing philosophies. They both wore running shoes with crampons, rather than heavier hiking boots, explaining that hauling extra pounds on your feet is no different than on your back. We could understand this better on this climb, because it was challenging lifting those heavy boots and crampons for 4 hours straight up! We were happy to have the rest of the gear, all of which we used, and which we were able to dump, mostly wet, in bins at the end, rather than needing to dry it all out ourselves for a day. This outfitter has been guiding climbs for years. As a matter of fact, our same four guides did the climb three to four times that same week. For us, however, we were thrilled to have made it to the top, and will consider it a once-in-a-lifetime experience!

Homeopathic and Dietary Preparation the Night Before the Climb

Volcán Villarrica is 2847 meters (9380 feet) high. Seasonally, including when we went, it is possible to ride a chairlift part way. The vertical ascent (think steep) is about 700 meters (2300 feet straight up). It has a gorgeous, perfectly conical form; has a diameter of 200 meters; and contains a permanent lava lake. It is definitely an active volcano, with eruptions about every 20 years, typically of a lahar (overflowing of lava from the crater which melts the glacier surrounding the crater and sends a combination of lava and hot water down the mountain into the river valley). The last eruption was in 1984. There have been few deaths, and the volcanologists pay close attention to the conditions. A fairly constant fumarole can be seen emanating from the crater (and from our front door). Locals assure us that as long as she is steaming, no worries! Each year's thousands of tourists set out to climb the volcano up to the crater, most of them successfully.

We've enjoyed our share of high-altitude hiking and touring, the highest a couple of years ago in the Atacama Desert in Northern Chile (17,000 feet), in Ecuador outside of Quito (and we plan to return in a couple of months to hike around Volcán Cotopaxi there, but not climb), as well as last June in the High Atlas Mountains in Morocco. We knew that it's no fun to suffer from altitude sickness. We were reminded of this by a neighbor friend here who spent three days in bed at his hotel because he felt so terrible. Embarking on our volcano trip, we were quite aware of homeopathic Erythroxylon's (from the coca plant) effectiveness for preventing these unpleasant symptoms (see our *Townsend Letter* column on hypothermia, February/March 2014). It is the same plant that is chewed ubiquitously by indigenous Peruvians, Bolivians, and Ecuadorians and available widely to Machu Picchu visitors. We have found the homeopathic preparation stronger and more rapidly effective. We take a dose either the night before or the morning of our arrival at the high altitude and have had no problems. Of course, it is more challenging if one remains at the altitude for more than 6 hours, which was not true in our case. We took one dose each of a 1M potency; however, 200C would have been quite adequate, and perhaps even 30C. The climb turned out to be challenging enough without having to deal also with altitude sickness.

Claudio and Suzy of Summit Chile advised us to drink lots of water the day before the climb and to eat a heavy pasta meal the night before the trip. That was no real hardship! They assured us that any possible weight gain due to the carb loading would be offset by the energy expenditure of the climb. They were right!

Thin Ozone Layer Protection

We have heard repeatedly that the ozone layer is depleted over Chile, and that the sun is more dangerous here compared with other parts of the world. A hole in the ozone layer does exist over the South Pole in the Southern Hemisphere. It does apparently pass over the Patagonia region of South America (4 to 5 hours south of Villarrica) from October to December, especially from 11 a.m. to 4 p.m. Especially vulnerable are Australia, New Zealand, Argentina, and Chile. In fact, Australia has the highest rate of skin cancer in the world. So, sunscreen was a must.

We researched the effectiveness of sunscreens when doing our investigation for *The Savvy Traveler's Guide* and found the Environmental Working Group (EWG; www.ewg.org) to be the most reliable source of information. It is only since 2010 that sunscreens are being carefully evaluated for both effectiveness and harmful side effects, including, ironically, cancer. According to the EWG, the US FDA was aware of the potential danger of some chemicals contained in sunscreens for as much as 10 years earlier, but did not take action. The main dangers are due to oxybenzone, a hormone-disrupting chemical that penetrates the skin and enters the bloodstream. Also of concern is retinyl palmitate, a form of vitamin A. The EWG discourages the use of products containing these substances. Its website provides ratings of the most popular sunscreens, with a particular emphasis on which are safe for babies and young children. It is an essential resource for parents.

Another concern is nano-sized titanium dioxide, which may have significant health implications. Also worthy ➤

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of consideration is the need for reliable information concerning SPF ratings, which are often misleading and meaningless, offering a false sense of security to sun worshippers.

Well informed from our book research, we slathered ourselves with BWC (Beauty Without Cruelty) Broad Spectrum SPF 30, a natural zinc oxide sunscreen. Forget about looking like a fashion plate when it comes to sunscreen: slather and get used to the white look.

We applied sunscreen generously to our faces, which were all that were exposed. And we did reapply once during the 4-hour ascent during a rest stop. What we didn't count on were drippy noses that removed the sunscreen from our lips. Nor did we remember to take the high-SPF lip sunscreen that we left at home with our ultralight backpacking gear. A big oversight, as we will share later!

A Grueling Ascent and an Exciting Descent

We are seasoned hikers, but not with crampons and full gear. Hiking is one matter and ascending a snow-covered volcano another, even if the climb, as in this case, was not a technical one. The ice axes, though a necessary precaution, were awkward. We were encouraged to climb in a tight group, placing our feet in the tracks of the person just ahead. That worked until Judyth fell about 100 meters behind, encouraged, gently but surely, the entire time by one of the guides. The weather conditions were perfect: sunny, with intermittent wind; we waited out for about 20 minutes at one point while sulfurous fumes emitted toward us from the crater. The relentless uphill ascent, demanding stamina and endurance, was rewarded by a spectacularly clear and panoramic view from the top, a moment of sacred silence invoking *Rukapillan*, "House of Spirits" in the Mapuche language, Mapudungun. Another alternative meaning is *Quitralpillán*, "Dwelling of Ancestors with Fire." The high-fives, awesome views, and memorable photos were well worth the effort. We were able to spend a good half hour at the time marveling at the 360-degree views of four other volcanoes, the surrounding Andes, and glacial lakes.

Our guides were ultracautious, instructing us in the correct use of ice axes, insisting on helmets all the way back to the van, and descending by foot, rather than by butt, the first third or so. Then the crampons came off and we engaged in what felt like an Olympic luge. We tucked the plastic ovals under our butts, attempted (only partially successfully) to slide down close to each other, and enjoyed the roller-coaster-like ride of our lives. Bouncy, to say the least; and, when we tried to walk crampon-free, we often ended up on our butts anyway. Nine hours after we gathered together in the early morning, all 15 or so climbers plus the 4 guides arrived back in Pucón. We returned exhausted, elated, and relieved.

The Worse for Wear

What was most surprising for us was that it took about 2 weeks to fully recover. We are 64 and nearly 67, and we still like to think of ourselves as invincible. Especially with the support of homeopathy and naturopathy! One of our Whidbey Island role models, Meg Petersen, is 87, still hiking, and just stopped backpacking a year ago. That is our hope for ourselves. (We plan, hopefully, to celebrate Bob's 65th birthday, a year and a half from now, to hike part of El Camino de Santiago de Compostela in Spain). Back to our recovery from the climb: Arnica, the homeopathic godsend for sore, overused, or injured muscles, was a great help, as were a great massage and daily soaks in our rooftop spa. Compared with any of our previous hikes, however, it took some time to get back into our grooves. We kept up with our regular classes of yoga, Zumba, and Pilates, beginning the following morning, rather than taking a break for a few days, which might have been a better idea. The sunscreen had worked well on our faces; however, we found that the wind and nasal dripping resulted in some peeling on the tips of and underneath our noses. The most unpleasant and uncomfortable symptom, for both of us, was lip burn. Homeopathic Cantharis helped, as well as Calendula and another herbal salve, but it took nearly 2 weeks for our lips to return completely to normalcy. On our upcoming trip to Cotopaxi, we will *not* forget our high-SPF lip balm! Are we glad that we finally climbed this volcano? Definitely. We feel a much more intimate relationship with its spirit, beauty, power, and wonder.

Judyth Reichenberg-Ullman and Robert Ullman are licensed naturopathic physicians, board certified in homeopathy. Their most recent book is *The Savvy Traveler's Guide to Homeopathy and Natural Medicine: Tips to Stay Healthy Wherever You Go!* Their previous books include *Homeopathic Self-Care, The Homeopathic Treatment of Depression, Anxiety and Bipolar Disorder, Whole Woman Homeopathy, Ritalin-Free Kids, Rage-Free Kids, A Drug-Free Approach to Asperger Syndrome and Autism, The Patient's Guide to Homeopathic Medicine,* and *Mystics, Masters, Saints and Sages: Stories of Enlightenment*. New editions of *Ritalin-Free Kids, Whole Woman Homeopathy,* and *Homeopathic Self-Care* are now also available as Kindle and iBook versions, as well as mini iBook versions of all of the books. The doctors live on Whidbey Island, Washington, and in Pucón, Chile, and practice at the Northwest Center for Homeopathic Medicine in Edmonds, Washington. They treat patients by phone and videoconference as well as in person. They can be reached at 425-774-5599, drreichenberg@gmail.com, or drbobullman@gmail.com; their website is www.healthyhomeopathy.com.

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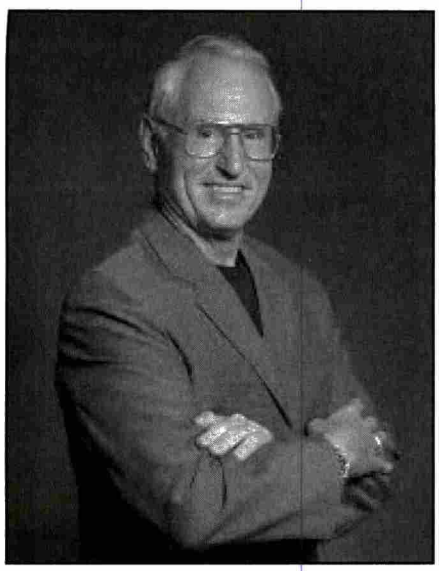

F.A.C.T. – Just the Facts

by Dr. Garry F. Gordon, MD, DO, MD(H)
Gordon Research Institute

Pueraria Mirifica: Nature's Safe Alternative to Estrogen Therapy

Menopause. The onset of this phase of life is marked by a decline in the production of estrogen – a hormone that serves as a chemical messenger in the body and regulates the menstrual cycle, controls breast development, and helps maintain healthy bones and a healthy heart. From puberty to menopause, the ovaries produce estrogen. Once menopause sets in, the ovaries no longer make estrogen, and body fat becomes the primary source for estrogen.

Estrogen is a vital key to healthy aging. But when a woman's body undergoes this important change, the accompanying symptoms can be severe enough to disrupt her life – and affect the lives of those around her. Hot flashes, night sweats, vaginal dryness and thinness, and frequent bladder infections are common complaints. Women also report chronic fatigue, weight gain, joint pains, bone loss, hair loss, insomnia, mood swings, memory loss, decreased libido, and a decrease in arousal and orgasmic response. Perimenopause also marks the beginning stages of increased risk of heart disease and osteoporosis.

Menopause is not a disease. It is a natural stage in a woman's life, and one that should be embraced and celebrated as a freeing and wondrous time – not looked upon with disdain and fear. Over the years, prescription and various herbal remedies have come and gone. Most have proved either too ineffective or too dangerous to be worth the risk. Sadly, many women continue to suffer needlessly due to the mainstream media's scare-tactic reporting about the serious and sometimes fatal side effects caused by hormone replacement therapy. It is true that most women will not enjoy optimal health after menopause or reach their maximum intended lifespan without hormonal support, and far too many physicians are *under*informed about estrogen supplementation and the risks of heart disease and breast cancer. I am here to tell you that healthy aging and all-natural, safe, and effective hormone replacement support is possible!

In Thailand, women have been finding relief from the symptoms of menopausal change for hundreds of years. They have found this relief in preparations from the root of a flowering plant that grows in abundance in their region. That plant is *Pueraria mirifica*, or Thai kudzu. My good friend Dr. Sandy Schwartz relocated to Thailand some 20 years ago, and shared with me how the native people had been using *Pueraria mirifica* for centuries, as both a food and as a part of their traditional medicine. As I explored further, I found that the lowest rate of breast cancer in the world was in Thailand's northern region – the only place in the world where *Pueraria mirifica* grows. Since that time, dozens of scientific studies have documented the beneficial and protective effects of this amazing plant.

Pueraria mirifica belongs to the same family of legumes that includes soybeans and peas, and contains a bounty of natural chemical compounds that foster good health. Most fall into a category called *phytoestrogens*. These naturally occurring chemical compounds have structures that are similar to estrogen. *Pueraria mirifica* is unique in that it is the only plant to contain a special phytoestrogen called miroestrol. Miroestrol is extraordinarily similar in structure and function to a type of estrogen called estriol. There are three types of estrogen in humans: estradiol, estrone and estriol. Of the three, estriol is the weakest. Its weakness, however, is actually its strength. Clinical trials have shown no links between estriol and cancer, and women who have taken it reported few side effects compared with those who took estradiol or estrone as hormone replacement therapies.

In her book *The Wisdom of Menopause*, Dr. Christiane Northrup states that *Pueraria mirifica*, the only kudzu variety containing miroestrol, is "hands down one of the most powerful supplements to take for menopausal symptoms. It is extremely safe and effective at relieving

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no fewer than twenty different conditions associated with menopause and perimenopause, including vaginal dryness, hot flashes, night sweats, depression, insomnia and irritability." Miroesterol has adaptogenic effects on bone and vaginal tissue, while also protecting the breasts and endometrium from the adverse effects of excess estrogen. PM is also shown to be effective in preventing osteoporosis in ovariectomized rats by increasing bone mineral density and bone mineral content. Many women are concerned and keen to prevent osteoporosis, but what is really exciting is that we have studies today proving that PM facilitates osteoblast and osteoclast reformation, effectively *reversing* bone loss.

Once just a promising plant that Asian women whispered about, *Pueraria mirifica* is now refined and formulated to the highest standards and is called Puresterol. Approved as a food supplement by the FDA, Puresterol is available from Longevity Plus LLC as H.R.T. Plus (Herbal Remedy from Thailand). H.R.T. Plus has been documented in extensive research to safely eliminate all menopause related symptoms while actually providing anticancer protections for the breast and other tissues. It is a SERM-beta (selective estrogen receptor modulator of the beta receptor) and provides favorable effects throughout the entire body. It protects against bone loss, depression, insomnia, hot flashes, vaginal dryness, and loss of memory. In my experience, there is no comparison between the minimal effects of traditional botanicals such as black cohosh, red clover or soy, and the dramatic benefits I have seen in my patients receiving Puresterol in H.R.T Plus.

With ever increasing numbers of women searching for safe, alternative, organic, and holistic remedies and approaches to breast and hormonal health and longevity, Puresterol is the perfect fit.

Here is a discussion on the safety and efficacy of bioidentical hormone replacement and breast cancer risk by F.A.C.T. forum participants (names and responses redacted to protect member confidentiality):

Q: What are people's thoughts on bioidentical estrogen use in a woman who has recent history of breast cancer?

I know it is obvious: no estrogen replacement yet I have three patients now who have read Suzanne Somers's books, saying that her doctor has researched this and says that post breast cancer patients do better with estrogen, even if their tumors were ER+, and that they have decreased risk of reoccurrence, even with bioidentical estrogens

This still seems crazy to me. ~RZ

A1: It's not crazy when one understands that low iodine may play a role in dysplastic breast cancer cells; iodine also plays a role in clearing estrogen from breast tissue in activating enzymes. Although I've not read Suzanne Somers's most recent book, my clients have referred to the information in it.

Looking at estrogen only as the primary cause for breast cancer does not seem to be the most comprehensive way to look at this disease once one understands the biochemistry of the breast tissue. I've picked up good information on this at conferences on measuring human hormones and on iodine as well as the current research on both. The problem is that in conventional medical practice we only know to focus on the "ER+" tissue and not the bigger picture. Keeping one's milieu on the alkaline side (avoid sugar, have adequate minerals to activate enzymes, detoxify heavy metals/other toxins, etc.) helps cells not become dysplastic as well.

"What Your Doctor May Not Tell You About Breast Cancer" by Drs. Lee and Zava, "Breast Cancer and Iodine" by Dr. David Derry are a couple good books to start one out. Also, attending ZRT Laboratory's conferences (http: www.salivatest.com) have helped me a lot over the years as well in learning from various physician speakers. I also see positive changes in breast thermograms when women balance their steroid hormones, normalize iodine levels, etc. ~CW

A2: It is not crazy. When you replace estrogen in a patient with breast cancer you should use only Estriol (bio-identical) which has never been implicated in cancer of the breast not Estradiol or Estrone (which have been implicated). Even though Suzanne Somers has some good information it is not without fault. I have Patients with history of breast cancer who are on the Estriol and I believe that they are at decreased risk of reoccurrence. Using the word Estrogen is misleading.

~FP

A3: Dear RZ,

Hot topic! Some very important points to remember about hormones.... First, all hormones are not the same. Second, each case is different. Third, look at the big picture, not just one factor. Allow me to explain. Hormones produced by the body are the natural ones that nature intended for the body. They have a certain biological activity. Let's say for argument's sake, they have an activity level of "x". In a perfect world where even our genetic predispositions are moderated correctly with nutrients and no pollution, disease (like breast cancer) would be rare. In today's world, women are exposed to xenoestrogens, synthetic estrogens (BCP, HRT), and animal estrogens (natural and synthetic) from our diet. All this overlies a woman's natural estrogens produced by her own ovaries. Considering all these hormones must be processed through the liver and or stored in adipose cells, the load can be great. The biological activity of synthetics and oxidized exogenous estrogens is much greater than "x" and I believe is

largely responsible for the detrimental estrogen overload diseases like breast cancer, fibroids, PMS, etc.....Since bioidentical hormones attempt to emulate natural estrogen more closely than the other types, there is likely a moderating effect happening in the body. To improve on this, phytoestrogens are an even better strategy. Phytoestrogens (from plants) have less biological activity than the above, but can still occupy estrogen receptors with about 1/400th the strength. The beauty of this is that the more powerful and hazardous estrogen forms are displaced, allowing them to be unbound and free to be eliminated via the liver. In a very toxic and estrogen-overloaded individual, even bioid hormones are probably having a moderating effect. Think about it. Case history will uncover the prescription hormones taken in the past or at least the high dairy-consuming vegetarians. Beware the plastic water bottles. Remember that cheese is a highly concentrated source of oxidized hormones. No matter what product you choose to add in a breast cancer survivor's protocol, look at her ability to get the bad hormones out. Hope this helps.

Sincerely ~TM

A4: Dear Doctor,
I hate beating the same drum about Pm. We are now completing a Pm study on the mechanism of action as to ER beta expression in the UK, which has already demonstrated no potential cancer proliferation on MCF-7 cancer cell lines. This confirms the studies that have preceded it. Our study should be ready for publishing sometime next year. If you would go to www.puresterol.com you will find many of the published articles, with a link to GordonResearch.com where additional studies can be found. There you will find a Phase I, Phase II and Phase III study; showing Pm alone is as beneficial as Premarin and Premarin with progesterone. In addition, there are articles on Pm's beneficial effects on circulation, bone density and cognition.

A new article, published this month in a rather obscure journal, tested a material identified *Pueraria mirifica* Graph Ex Benth. There is no such species. It's actually identified as Pueraria candolii Graph Ex Benth and this species is among 12 other Pueraria sub-species erroneously being sold in the market as Pm. It was shown to act in a very similar manner to estradiol, with all the negative implications, which Pueraria candolii, var mirifica Airy Shaw et Suvat has no such negative actions. ~SS

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A5: Refer to the very thoughtful article recently published on FACT regarding this issue. I forget the doc's name but it was a 3-4 page article that explored estrogen replacement and breast cancer. You should read that.
~RW

A6: If breast cancer occurred because of estrogen, my 13 year old daughter would have it now that she has started her periods. Luckily most in this group get "it" the it being that cancer is multifactorial and the fact that some MD (most likely) decided that because a tumor has markers associated with estrogen, doesn't mean it was caused by it. I have a friend who had breast cancer at 35 and they didn't do a hysterectomy because she was still producing estrogen. It is a huge risk from a legal standpoint, but most likely estrogen has very little to do with breast cancer other than most br. cancer is in women who have high estrogen levels comparatively. the hard part is figuring out what is the real problem. ~JB

A7: My experience with this is that the use of DIM really makes a difference. It changes the estrone metabolites to be more protective, and can reduce the risk of future incidence of breast cancer, even if no exogenous estradiol is used. I have given estradiol to my women patients who have had breast cancer, using it topically only, along with good opposition of progesterone, taken orally. Oral administration of progesterone produces better sleep. It's a GABA effect. Check labs often. Genova also has a test to check Estrogen Metabolites which can be checked before and after using DIM for a few months. I keep everyone on it for prevention regardless of the test results.

I also give Calcium d'glucarate to women who have had breast cancer that are going to use bio-identical HRT. Dose is 500 mg. bid. DIM dose is 100-200 mg. qd. DIM is also found to be good for preventing colon, lung, ovarian Ca in women, and colon, lung, breast and prostate Ca in men, and is a must for anyone with any of these cancers in my experience. High lignan flax is a 3rd very good protectant. Hope this is helpful. ~MM

A8: Dear RZ,
Sure, prescribing ERT after breast cancer is highly dangerous to prescribers, due to massive vested interests against what is appropriate and cheap, and to hysteria and disinformation from the WHI, MWS, EPIC and other misguided studies. It has taken over 5 years for "authorities" in USA - the WHI, AMCOG, NAMS- to recant their untenable beliefs and prejudices from the WHI, admit that the International Menopause Society www.IMSociety.org and the Nurses' Study were right all along, that there is no reason to avoid appropriate HT, or stop it at 60 years.

But the use of appropriate HRT has always done vast good, and rarely significant harm, eg in the WHI ERT-only trial 2004 master paper, in women in their fifties on "appropriate" ET for >6yrs, the incidence of both BRCA and all major disease, and mortality, fell by 1/3. Ditto with conservative estrogen-progestin dose for 9 years in such women in the Oulu trial by Heikinnen ea 2006. Ditto in the NBCCT (Bernard Fisher in the 1990s). Because of phobias, myths and vested interests, further meaningful trials of the best appropriate HRT ie bioidentical human hormones (as is gold standard in all of endocrinology including testosterone replacement in men) in women after breast cancer is unlikely -who will fund these?

But ethical practitioners have a duty to practice evidence-based medicine that is best for their patients- including where necessary appropriate HT. It takes a martyr, a death wish, to put the interests of patients first and risk prosecution for advising appropriate balanced HRT in cancer patients. Certainly no sensible surgeon or oncologist dare publically support such heresy, because the best HRT prevention cannot avoid some cancers and early deaths (albeit far fewer) occurring- and they are the ones who may have to do further surgery/ oncology therapy.

Remember that "Authorities" in Vienna murdered Dr Semmelweiss for doing and preaching what was right (history says they strangled him); and USA "Authorities" mercilessly persecuted nuclear advisor Richard Barlow, nurse Margaret Sanger, Drs Jonathan Wright and Guylaine Lanctot for doing what was right. Boldness be your friend. Read Illich' Medical Nemesis, Elaine Feuer's The FDA's War against Patients, Dr James le Fanu's The Rise and Fall of Modern Medicines, John le Carre's The Constant Gardner, McTaggart's What Doctors Don't Tell You; Naomi Klein's Shock Doctrine-Disaster Capitalism; Al Gore's The Assault on Reason; and Levine +Scott-Clarke's The Pakistan Deception.

It is now common cause that the main trigger for activating dormant breast cancer nests is progestin: in the premarin-only arm of the WHI (2004), there was 28% lower incidence of invasive BRCA in the women aged 50-69 at start (and 44% less CHD, 36% fewer deaths in the women starting under age 60y); so the feared major ADVERSE endpoints after HRT - athero/ thrombosis, and breast cancer- are largely related to progestin, age of onset of HT, and dose.

Prof Fred Naftolin of NYU- former head of ObGyn and then professor in Biology at Yale has a (not the) final word below: don't quibble over the type or route of estrogen, or what has/ has not been "proven" by big medium-term trials. It is easy to see the wood and the trees. Only oral estrogen has been proven (in >5year

trials) to do wonders in reducing morbidity and mortality long-term, even from breast cancer (in the WHI 2004 paper on solo oral conjugated equine estrogen CEE when started appropriately from menopause; the 1990s Breast and Colon Cancer trial- Dr Bernard Fisher ea; and the Oulu trial 2006 with oral estradiol +- synthetic progestin). Similarly, physiological systemic testosterone replacement has shown if anything an antiproliferative effect on breast tissue in trials in both women (Zhou & Dimitrikakis); other primates (Clarkson; Zhou & Dimitrikakis); and rodents (von Schultz).

The landmark Wake University primate trials (Clarkson ea 1995-2007) show the CVD benefits of early postmenopausal (but not late) systemic estradiol plus progesterone, and oral CEE but not synthetic progestin; but adverse effect of oral CEE on breast proliferation. Significant medium - and long-term benefit has not yet been shown for a single plant-sourced phyto-estrogen in controlled trials in postmenopausal women- and who is going to fund such a trial since both kava and black cohosh have killed when used for menopause symptoms.

The current KEEPS trial under way (Harman, Naftolin ea) will soon show what balance of benefit and harm there is between 450mcg a day oral premarin or 50mcg a day estradiol patch or placebo, (with or without parenteral progesterone) in young postmenopausal women. This trial, in women well under 60yrs, albeit (in comparison with the WHI) small and only for 5 years, will to a great extent largely resolve the unwarrantedly acrimonious secondary debate over oral vs parenteral and human bioidentical vs oral xenohormone ie horse estrogen. Unlike the obvious difference (seldom subtle) between good and bad, there are many good alternative routes to Rome or health, the differences being mostly superficial – like between man and woman.

It is common cause that the main trigger for activating dormant breast cancer nests is progestin, so in the premarin-only arm of the WHI, there was 28% lower incidence of invasive BRCA in the women aged 50-69 at start (and 44% less CHD in the women starting under age 60y;) so breast cancer after HRT is very much age dependent.

This benefit has not yet been shown for a single plant-sourced or synthetic estrogen- and who is going to fund it since the 1950 trial of synthetic estrogen (diethylstilbestrol) is still causing increased breast cancer in the women who received it (and vaginal cancer in their daughters, and infertility in their grandchildren). ~NB

A9: Dear RZ,
I agree with your sentiments. However, so-called "bioidenticals" have no magical differences from their natural or synthetic counterparts, except they often suffer from lack of quality control and scientifically investigated regimens. Estrogen has an enviable record in treatment of the post-BRCA subject. Their prognosis is ~ the same as being one clinical stage lower. Replacement hormones should not be used in women with active BRCA; rather the hormones should be part of an integrated program of treatment of the post-BRCA subject. Regards ~FN

A10: I don't have the answer, but here is some additional information. At the last ACAM meeting, Dr. Drisko (who's running the U Kansas IV vit C trials) mentioned that she had a patient with breast cancer (I don't recall the ER status) whose cancer took off suddenly and admitted that she convinced another doctor to give her bioidentical estrogen (maybe just estriol). I heard of a paper in the 1970s (?) published in JAMA called something like "Estriol: the forgotten estrogen" that mentioned in a footnote that someone gave estriol to some women with breast cancer and it went away. Finally, there are a few studies and meta-analyses about estrogen replacement after breast cancer and the risk of recurrence, which seem to lean toward no increased risk of recurrence after a successfully treated cancer (again no word on ER status), however this is after the cancer is gone. So, while there may be a little data showing it's OK, there's also some data saying it isn't. I'd be awfully careful and make sure the patient is fully informed about all her options and the lack of data. Remember that if she gets a relapse or gets worse, even if she was totally the one pushing for it, if she can't testify then the family left behind may seek a legal settlement. I hate to bring up scare stuff like that, but that's where we're living.
~MS

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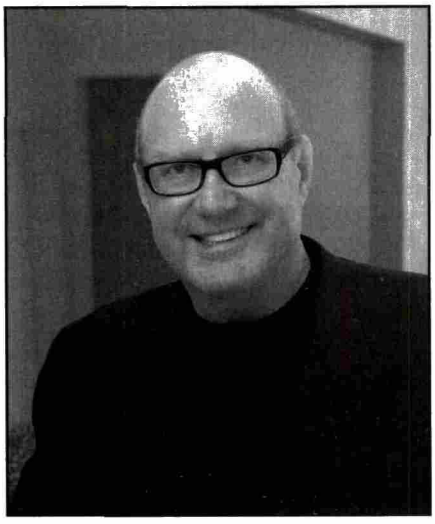

Monthly Miracles

by Michael Gerber, MD, HMD
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Nevada Homeopathic and Integrative Medical Association 2014 Conference: Part 2

William Henry Andrews, PhD: 'Live Forever or Die Trying': Is Aging Treatable?

Dr. Andrews is an internationally acclaimed molecular biologist who graduated with his PhD in molecular and population genetics in 1981 from the University of Georgia. He was the director of molecular biology at Geron Corporation in Menlo Park, California, and holds the patent for mammalian telomerase along with 43 other patents. Plus scores of scientific papers created in over 33 years in biotech research with research colleagues receiving the Nobel Prize. Currently he lectures internationally and is the founding president and CEO of Sierra Sciences in Reno, Nevada.

Health and Life Extenders

Life expectancy has increased from 47.3 year to 78.0 years since 1900. Better sewage systems, vaccines, refrigeration, exercise, cleaner water, better diets, antibiotics, better dental care, blood pressure medication, coronary artery by-pass surgery, cholesterol medications, chemo and radiation therapy, antioxidants, the antismoking crusade, better working conditions, controlled indoor environment, eyeglasses, and pasteurization are some of the reasons that Andrews offers. "But are we just creating sick old people?"

Efforts Under Way to Cure Aging

Stem cell, SENS (Strategies for Engineered Negligible Senescence Research Foundation), gene regulation, mitochondria support, brain uploading, nanomedicine, telomeres, cryonics, and others. "We need them all!"

Theories on Why We Age

Disposable Soma Theory: We just temporarily house our genes.
Oxidative Stress Theory: Free radicals cause damage to cells.
Vital Substance Theory: A vital substance is limiting.
Genetic Mutation Theory: Accumulations of mutations cause aging.
Reproductive Exhaustion Theory: After reproduction we die rapidly.
Aging by Design Theory: Aging is programmed.
Mitochondrial Dysfunction Theory: Altered mitochondria.
The Neuroendocrine Theory: Changes in hormone regulation.
Wear and Tear Theory: Self explanatory.
The Rate of Living Theory: Similar to the vital substance theory.
The Waste Product Accumulation Theory: Self explanatory.
The Cross-Linking Theory: Proteins such as collagen cross-link.
The Immune System Theory: Decreased immune function.
Errors and Repairs Theory: Inaccurate repair of damage.
The Order to Disorder Theory: Decreased maintenance of order.
Telomere Theory of Aging: Telomere length controls aging.
"They Are All True!"

Andrews likens it to multiple sticks of dynamite. Which stick of dynamite has the shortest fuse?

Telomere-Shortening Diseases

DNA chromosomes contain 100,000,000 bases. Telomeres, the plate where DNA lines up to divide, contain 16,000 bases, with 50 to 100 bases shortened with each division. When the telomere is shorter than 5000 bases, DNA stops dividing. At conception, we have 15,000 bases and by age 5 years it is down to 10,000 bases. Some people are born with short telomeres, such as children with progeria, who have a life expectancy of 20 years. Preventing telomere shortening could save these children's lives.

Telomere length affects almost everything, including cancer, cardiovascular disease, AIDS, Alzheimer's, osteoporosis, stem cells, skin care, pets, medical research, and aging. Andrews thinks that telomere measurement is best suited for population studies and not yet good for individuals. His laboratory measures telomere length by quantifying the terminal restriction fragment (TRF), Q PCR, fluorescence in situ hybridization (FISH), flow FISH, HT Q-FISH, and universal STELA to determine short telomeres. Obviously, complex laboratory measurements.

Preventing Accelerated Telomere Shortening

Vigorous aerobic exercise has been shown to lengthen telomeres, as evidenced by the German National Track and Field Team's telomere measurements. Longer leukocyte telomeres are associated with ultraendurance exercise independent of cardiovascular risk factors. Walking the walk, Bill Andrews is an ultramarathoner.

Other things we can do now to prevent telomere shortening are to exercise; take antioxidants, omega-3s, and vitamin D3; don't smoke; don't be obese; reduce stress; reduce depression; reduce pessimism; and be happy!

Aging doesn't occur in reproductive cells, and telomeres don't shorten in them.

Telomerase

Telomerase is the enzyme that inhabits the end of the telomere and is sometimes likened to the plastic cap on a shoelace. With each DNA division, telomerase also shortens and, when too short, can't initiate division. Some species don't have telomere shortening but die of other issues such as oxidation. One mollusk lived to 507 years.

On November 6, 2007, the first telomerase inducer ever was discovered and independently verified at Andrews's lab. His Sierra Sciences has screened over 300,000 compounds with over 900 hits to lengthen telomerase. Additionally, it has screened over 10,000 natural products with 37 positive hits with some already on the market. Andrews thinks that the telomerase issue should be solved in the next year!

Our theoretical maximal lifespan is 125 years, and lack of telomerase causes cancer.

Look for Andrews in an upcoming feature film called *The Immortalists* opening this year. Contact Sierrasciences.com for more information and read his book, *Curing Aging*.

Terry Pfau, DO, HMD: Homeopathic Treatment of Autism Spectrum Disorder

Dr. Pfau graduated from the Kirksville College of Osteopathic Medicine in 1985. He has studied with Rajan Sankaran, Roger Morrison, and Nancy Herrick and completed the UCLA Medical Acupuncture for Physicians course, among many other accomplishments. Pfau has taught for the British Institute of Homeopathy and is a past member of the Nevada Board of Homeopathic Medical Examiners. He practices in Las Vegas.

Prevalence

In 2000, the incidence of autism spectrum disorder (ASD) was 1 in 150. In 2010 it was 1 in 68. One in 42 boys and 1 in 189 girls were diagnosed, according to the Autism and Developmental Disabilities Monitoring (ADDM) Network, combining data from all sites.

Causality

Pfau asserts that the cause of autism is multifactorial and includes heavy-metal toxicity, especially mercury in vaccines and amalgams; problems with methylation; vaccines too early and too many; medications used during pregnancy or during delivery; emotional trauma either in utero or after birth; and repeated antibiotic use.

Appearance

ASD is characterized by profound failure to develop social relationships, deficiency in verbal communication, and compulsive or ritualistic behavior. The child resists cuddling and holding and seems to prefer playing alone – retreats into his or her own world, has poor eye contact, and lacks facial expression. S/he doesn't express emotions or feelings and appears unaware of others' feelings and inappropriately approaches a social interaction by being passive-aggressive or disruptive. The child fails to respond to his or her name or appears not to hear you at times.

In communications, s/he doesn't speak or has delayed speech, or may lose previous ability to say words or sentences and can't start a conversation or keep one going. They may speak with an abnormal tone or rhythm – using a singsong voice or robotlike speech and may repeat words or phrases verbatim but don't understand how to use them. They don't appear to understand simple questions or directions.

Compulsive behaviors include performing repetitive movements such as rocking, spinning, or hand flapping, and damaging activities such as head banging. Moving constantly, they may become fixated on an object with abnormal intensity and can become fascinated by details of an object such as the spinning wheels of a toy car.

Classical Homeopathy Single Remedy

Homeopathy works on a much deeper level than is accessible with diet, nutrition, or behavioral approaches. Food allergies often are healed. It takes time, usually years.

Tarantula. This remedy demonstrates excess energy. The patients are restless, quick in their motions, impatient. Better when they listen to loud rhythmical music and when dancing. When they get angry, they can become intense, impatient, and compulsive.

Chamomilla. These children are overly sensitive to an extreme degree; oversensitivity and irritability run through the whole symptom picture. Great irritability is worse with touch or being spoken to during pain, and they cannot bear to be looked at. They are capricious and want to be carried and rocked.

Belladonna. In Belladonna, we see intensity. This intensity is expressed as rage, violence, biting people or objects, pulling hair, spitting, and kicking. Congestion with heat of head, red face, cold extremities are cardinal signs of this remedy.

Nux Vomica. These individuals are excited, impatient, quick to act, very irritable, angry, and easily offended, and they may become violent. They can be jealous and oversensitive to noise, music odors, and light.

Tuberculinum. These patients are passionate, excited, discontented, desiring change, with grinding of teeth. Children are hyperactive, with behavior disorders, obstinate, disobedient, destructive, malicious with temper tantrums during which they strike and break things. They fear cats and dogs. ➤

Monthly Miracles

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Lycopodium. Great for digestive disturbances.

Strammonium. Anger, sees visions.

Anacardium (without a heart). Pfau cites two types. (1) Cruel, unfeeling, malicious, sadistic. (2) Helpless, hopeless, pleading, needy, insecure. This child thinks that s/he has two wills opposing each other, and desires to curse. The patient can be malicious, mischievous, and wicked with a sudden loss of memory.

Lac Caninum (dog milk). These patients have very low self-esteem and they think that nobody needs them in the family and that everybody looks down upon them. They have fear of failure. This lack of confidence could come from abuse in childhood, especially sexual abuse. The Lac caninum individual is obsessed with the idea that s/he is dirty, morally degraded, which can lead to obsessions and compulsive acts of washing. It can also manifest as hatred, rage, cursing, and malicious behavior.

Lyssin (saliva from a rabid dog; isn't homeopathy interesting?). Lyssin is similar to Lac caninum, with an extreme lack of confidence, irresolution, and easily offended and humiliated. They can also be abusive, rude, and display cursing and rage. Those needing Lyssin have more hard-heartedness and cruelty in their behavior and believe that they have suffered undeserved torture from their closest friends and relatives. They feel an intense moral anguish after becoming violently angry and can have a quick repentance.

Sensitivity of the Brain of a Baby

Babies receive a genetic transfer of information and a material transfer. Pfau thinks that every substance can cause energetic transfer or imprinting. These imprints are not only from direct damage by vaccination, a disease, or emotional trauma but can also be transmitted from the parents to the unborn child. He notes a great increase in the number of recommended, required, vaccinations between 1994 and 2010. This number increased from 8 to 15 vaccinations in babies. In Japan, the number of severe neurological reactions and deaths from DPT vaccinations was remarkably reduced when they gave the vaccinations at 24 months instead of starting at 3 months. In the period of 1970–1974, there were 57 severe neurological reactions and 37 deaths. After the change in 1981–1984, there were 5 severe reactions and 2 deaths.

Antibiotic toxicity can be antidoted by giving Poli-antibioticum 30C, 200C, 1M and 10M. He gives 30C twice per week then 200C twice per week then 1M twice weekly and finally 10M twice per week. To reverse tobacco exposure, he gives homeopathic Tobaccum. Roundup in GMO foods is 100,000 times more damaging to the infant brain. Glyphosate (Roundup) is available on BioMeridian and other EAV devices to make antidotes for this amazingly toxic herbicide.

Principles of Detoxification

Pfau believes that it is important to use each potency of the remedies. Do not move to a higher potency if the second dose still elicits reactions. In deep-seated pathology such as epilepsy, it is best to use an 8-week course. Repeat every potency twice a week for 2 weeks. Between different courses of detoxification, wait 2 weeks to see if the new situation is stable. If the child's symptoms are better but not completely gone, repeat the same course. If after a repeated course there is no further improvement, then no further repetition is necessary and move up in potency. If there is a relapse during this pause, then restart the same detoxification. When the course has to be repeated, there needs to be continued administration of the same potency whenever there is a reaction.

Often when there is a stronger detox reaction, more progress is made. Generally a reverse order of toxins is used, with the most recent causation treated first. But also the most probable and striking causation can be detoxified first. For example, start with the most recent vaccine and work backward and then address drugs taken during pregnancy. Generally, finish detoxification first, then go to classical homeopathy to complete the process if necessary. Sometimes a well-chosen homeopathic remedy can be given in between or along with detoxification courses.

Cleansing reactions can consist of a flare-up of emotional symptoms such as rage; tantrums; discharges from ear, nose, or throat; increased perspiration; eczema; diarrhea or constipation; difficulty with concentration; regression of language; and fatigue.

Specific Autism Remedies and Orthomolecular Treatment

Hydrogenium. It gives the capacity to connect people again with their essence, who they really are.

Saccharum. Stimulates social/emotional skills. Saccharum D6 to help heal the digestive system.

Cuprum. Helps heal obsessive tendencies and to make the patient more flexible and relaxed, capable of coping with stress.

Ascorbyl palmitate, 1000 mg 2 or 3 times per day. Fish oil 500 mg twice per day. Ascorbate complex 1000 mg 3 times per day with potassium, 60 mg magnesium, 3 mg zinc, and 75 mg bioflavonoids.

Added together to make a complete supportive program of detoxification, isotherapy, classical homeopathy, behavioral therapy, craniosacral therapy, diet, and nutrition are the missing pieces for autism.

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Calendar View complete calendar at townsendletter.com

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.

APRIL 9-12: NATIONAL AYURVEDIC MEDICAL ASSOCIATION 15th ANNUAL CONFERENCE in Newport Beach, California. CONTACT: www.ayurvedanama.org/page/NAMA15Anniversary/?

APRIL 10-12: SOUTHWEST CONFERENCE ON BOTANICAL MEDICINE in Tempe, Arizona. Psychiatric medication alternatives, insomnia, cannabinoids, PTSD. CE credits. CONTACT: 541-482-3016; www.botanicalmedicine.org

APRIL 11: ORGANIC ACIDS WORKSHOP: An Invaluable Tool for Discovering the Underlying Causes of Chronic Illness with Kurt Woeller, DO in Chicago, Illinois. Also, **MAY 2** in Washington DC. CONTACT: www.greatplainslaboratory.com/home/eng/OATworkshop.asp

APRIL 11: BASTYR UNIVERSITY presents NW HOMEOPATHS' CURED CASE CONFERENCE – MANY PATHS, ONE SIMILLIMUM in Kenmore, Washington. CONTACT: 425-602-3152; www.bastyr.edu/civicrm/event/info?id=1459&reset=1

APRIL 17-18: STRESS SYMPOSIUM: BEYOND ADRENAL FATIGUE in Atlanta, Georgia. CONTACT: www.a4m.com/2015-04-atlanta-stress-symposium.html

APRIL 17-19: CHELATION THERAPY CONFERENCE in St. Pete Beach, Florida. CONTACT: 800-430-9328; www.chelation2015.com

APRIL 18-19: CALIFORNIA NATUROPATHIC DOCTORS ASSOCIATION SPRING MEETING-ENDOCRINOLOGY in Marina del Ray, California. CONTACT: endoanp.org/conference.html

APRIL 20-JULY 26: COMPREHENSIVE TRAINING COURSE ON ACUPUNCTURE FOR PHYSICIANS (Phase 1 & 2) HOME STUDY & HANDS-ON PRACTICAL CLINICAL in San Francisco, California. AMA PRA Category 1 credits. CONTACT: 415-731-1330 or 888-882-1330 (toll free); www.acupuncturecourse.org

APRIL 23-26: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE INSTRUCTIONAL COURSES in Dallas, Texas. CMEs. CONTACT: www.aaemonline.org/courses.html

APRIL 23-26: 18TH CLINICAL APPLICATIONS FOR AGE MANAGEMENT MEDICINE in Orlando, Florida. CONTACT: www.agemed.org; conference@agemed.org

APRIL 23-26: AMERICAN ACADEMY OF MEDICAL ACUPUNCTURE 27th ANNUAL SYMPOSIUM in St. Louis, Missouri. CMEs. CONTACT: www.medicalacupuncture.org/ForPhysicians/Symposium.aspx

APRIL 24-26: 44th ANNUAL INTERNATIONAL ORTHOMOLECULAR MEDICINE TODAY CONFERENCE in Toronto, Ontario. Thirteen internationally-known physicians and researchers present on advances in orthomolecular psychiatry, oncology, cardiology, and general medicine. CONTACT: 416-733-2117; www.csom.ca/omt-2015-registration/

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

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

APRIL 27-MAY 1: MINDFUL PRACTICE ADVANCED WORKSHOP : ENHANCING QUALITY OF CARE, QUALITY OF CARING, AND RESILIENCE in Batavia, New York. For healthcare practitioners. Also, **OCTOBER 14-17**. CONTACT: www.urmc.rochester.edu/family-medicine/mindful-practice/presentations-workshops.aspx

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

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

MAY 1-3: 59th ANNUAL NORTHWEST NATUROPATHIC PHYSICIANS CONVENTION – Wisdom of our Elders in SeaTac, Washington. CONTACT: www.nwnpc.com/

MAY 1-3: 14th INTERNATIONAL CONFERENCE ON CONSCIOUSNESS IN AYURVEDA & YOGA in Edison, New Jersey. CONTACT: aapna.org/conferences/may-1-3-2015-edison-nj-usa

MAY 4-6: 12th ANNUAL NUTRITION & HEALTH CONFERENCE @ Arizona Center for Integrative Medicine in Phoenix, Arizona. CONTACT: nutritionandhealthconf.org/

MAY 6-9: 23RD ANNUAL WORLD CONGRESS ON ANTI-AGING MEDICINE in Hollywood, Florida. CONTACT: 888-997-0112; www.a4m.com/anti-aging-conference-2015-hollywood.html

MAY 8-10: ICMART XVII WORLD CONGRESS ON MEDICAL ACUPUNCTURE in Bali, Indonesia. CONTACT: icmart.org/events/upcoming-icmart-congress/upcoming-icmart-congress.html

MAY 8-10: 10th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE in Philadelphia, Pennsylvania. CONTACT: www.homeopathycenter.org/2015-joint-american-homeopathic-conference/

MAY 10-14: GERSON THERAPY PRACTITIONER TRAINING-MODULE 1 (of 2) in San Diego, California. In-depth training in Dr. Max Gerson's dietary healing principles. CONTACT: 800-838-2256; aonken@gerson.org; gerson.org/gerpress/practitioner-training/

MAY 16: PATH FOUNDATION presents THE SECRET WEAPON & THE WAR ON DRUGS: BRAIN RESEARCH in New York City, NY. CONTACT: 646-367-7411; www.pathfoundationny.org

MAY 28-30: INSTITUTE FOR FUNCTIONAL MEDICINE 2015 ANNUAL INTERNATIONAL CONFERENCE in Austin, Texas. CONTACT: https://www.functionalmedicine.org/conference.aspx?id=2858&cid=0&section=t433

MAY 29-JUNE 1: MEDICINES FROM THE EARTH HERB SYMPOSIUM in Black Mountain, North Carolina. CE credits available. CONTACT: 541-482-3016; www.botanicalmedicine.org

MAY 30-31: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION 2015 SPRING CONTINUING MEDICAL EDUCATION CONFERENCE in Scottsdale, Arizona. CONTACT: www.aznma.org/2015/02/aznma-spring-2015-conference/

MAY 31- SEPTEMBER 12: COMPREHENSIVE TRAINING COURSE ON HERBAL MEDICINE FOR PHYSICIANS (Stage A & B) PREPARATORY PROGRAM & PRACTICAL SESSIONS in San Francisco, California. AMA PRA Category 1 credits. CONTACT: 415-731-1330 or 888-882-1330 (toll free); www.acupuncturecourse.org

JUNE 5-7: NEURAL PROLOTHERAPY WORKSHOP in Seattle, Washington. CONTACT: Jeff Harris, ND, 206-517-4748; www.jeffharrisnd.com

JUNE 5-7: HOMEOPATHY RESEARCH INSTITUTE 2015 CONFERENCE – Cutting Edge Research in Homeopathy in Rome, Italy. CONTACT: www.HRIRome2015.org

JUNE 11-14: FOOD AS MEDICINE – CENTER FOR MIND/BODY MEDICINE in Minneapolis, Minnesota. Also, **SEPTEMBER 18-22** in Stockbridge, Massachusetts. CONTACT: cmbm.org/professional-trainings/food-as-medicine/

JUNE 11-14: MEMBRANE MEDICINE INTERNATIONAL SYMPOSIUM in Las Vegas. Addressing Epigenetics, the microbiome and the brain with lipid therapy. Intensive Clinical PK Biomedical Course. CONTACT: NeuroLipid Research Foundation, 856-825-8338; fax 856-825-2143; www.neurolipid.org/our-focus/membrane-medicine-biomedical-conference-series/

JUNE 12-14: 12th INTERNATIONAL HERB SYMPOSIUM in Norton, Massachusetts. CONTACT: www.internationalherbsymposium.com/index.php?route=common/home

JUNE 25-26: SopMED (Society of Oxidative and Photonic Medicine) INAUGURAL TRAINING AND CONFERENCE in Salt Lake City, Utah. Ozone/UBI training and business workshops. Limited enrollment. CONTACT: 517-242-5813; www.sopmed.org; info@sopmed.org

JUNE 25-28: HEALTH FUSION – CANADIAN ASSOCIATION OF NATUROPATHIC DOCTORS NATIONAL CONFERENCE in Calvary, Alberta, Canada. CONTACT: https://www.cand.ca/Conference_Health_Fusion.healthfusion.0.html

JULY 4-5: WORLD CONGRESS ON NATURAL MEDICINE in Havana, Cuba. Sponsored by The Sacred Medical Order. Contact: www.smoch.org; email: panamint@sisterisles.kn

JULY 17-19: 21st ANNUAL INTERNATIONAL INTEGRATIVE MEDICINE CONFERENCE in Melbourne, Australia. CONTACT: https://www.aima.net.au/21st-annual-international-integrative-medicine-conference/

AUGUST 3-5: 3rd INTERNATIONAL CONFERENCE & EXHIBITION ON TRADITIONAL AND ALTERNATIVE MEDICINE in Birmingham, United Kingdom. CONTACT: traditionalmedicine.conferenceseries.com/

AUGUST 5-8: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS (AANP) 30th ANNIVERSARY CONFERENCE in Oakland, California. CONTACT: www.naturopathic.org/aanp2015

AUGUST 21-23: INTEGRATIVE ADDICTION 2015 in Myrtle Beach, South Carolina. CONTACT: 954-540-1896; Sharon@integrativeaddiction2015:com; integrativeaddiction2015.com

SEPTEMBER 11-13: THE GATEWAY FDTN. FOR BIOLOGICAL & INTEGRATIVE MEDICINE presents CURING THE INCURABLES in St. Louis, Missouri. CONTACT: iamconf.com

SEPTEMBER 14-15: 15th INTERNATIONAL CONFERENCE ON AYURVEDIC MEDICINE in Paris, France. CONTACT: aapna.org/conferences/15th-conference-september-2015-paris-france

SEPTEMBER 17-20: AMERICAN ACADEMY OF PAIN MANAGEMENT 26th ANNUAL CLINICAL MEETING in Washington, DC. 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 18-29: 16th INTERNATIONAL CONFERENCE ON AYURVEDA & PSYCHIATRY in Vevay, Switzerland. CONTACT: aapna.org/conferences/16th-conference-september-18-19-2015-switzerland

SEPTEMBER 25-27: 3rd ANNUAL LIFESTYLE MEDICINE SUMMIT in Phoenix, Arizona. CONTACT: https://www.metagenics.com/events/2015_lifestyle_medicine_summit

SEPTEMBER 25-27: WORLD FEDERATION OF ACUPUNCTURE-MOXIBUSTION SOCIETIES INTERNATIONAL CONFERENCE in Toronto, Ontario, Canada. CONTACT: wfastoronto2015.com/

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

OCTOBER 9-11: 17th INTERNATIONAL CONFERENCE ON AYURVEDA & AUTOIMMUNE DISORDERS in San Jose, California. CONTACT: aapna.org/conferences/17th-conference-october-9-11-2015-san-jose-ca-usa/

OCTOBER 24-29: 16TH ANNUAL SCIENCE AND CLINICAL APPLICATION OF INTEGRATIVE HOLISTIC MEDICINE in San Diego, California. CONTACT: www.scripps.org/for-health-care-professionals__continuing-medical-education-cme

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; phone (250) 490-3318; fax (250) 490-3348; support@oirf.com; www.oirf.com ◆

Study Shows Taking Sustamine L-Alanyl-L-Glutamine After Strenuous Exercise May Increase Cognitive Function

Taking Sustamine L-alanyl-L-glutamine after endurance exercise increases athletes' reaction times and cognitive function when compared with no hydration, according to a study published in the *European Journal of Sport Science*.[1]

Twelve male athletes performed four endurance trials of various lengths. One trial allowed no hydration, with another consisting of consumption of an energy drink. The other two trials included low and high doses of Sustamine in energy drinks.

Participants were then given a reaction time test where they had to press buttons as quickly as possible when lit up with either a hand or foot. With no hydration, researchers found that athletes' reaction time was actually negatively affected while those taking Sustamine saw a noticeably higher number of correct hits.

For cognitive tests, participants were required to subtract the number 7 from a random four-digit number. The number of correct answers was recorded. Nonhydrated subjects had correct answers as high as 5.02; those who ingested Sustamine had correct answers as high as 5.96 to 7.3.

To view the entire study, visit http://www.tandfonline.com/doi/full/10.1080/17461391.2014.969325#.VG-27PnF9SI.

Sustamine is a dipeptide of glutamine that provides several substantial benefits such as enhanced recovery, immune system support, and increased metabolic rate. On top of these benefits, research suggests that Sustamine is absorbed more than 240% better than standard L-glutamine. This means that you get results while having to use less.[2]

Notes

1. Pruna GJ, Hoffman JR, McCormack WP, et al. Effect of acute L-Alanyl-L-Glutamine and electrolyte ingestion on cognitive function and reaction time following endurance exercise. *Eur J Sport Sci*. 2014 Oct 16:1–8. Epub 2014 Oct 16. doi:10.1080/17461391.2014.969325.
2. Harris RC et al. NBH: L-glutamine absorption is enhanced after ingestion of L-alanylglutamine compared with the free amino acid or wheat protein. *Nutr Res*. 2012. doi:10.1016/j.nutres.2013.02.003.

About Sustamine

Sustamine L-alanyl-L-glutamine is a stable dipeptide of L-alanine and L-glutamine. Sustamine is more easily absorbed by the body than complex protein molecules. This makes Sustamine a highly effective ingredient for hydration, endurance, and recovery.* Vegetarian, allergen-free, and the only GRAS L-alanyl-L-glutamine, Sustamine is also tasteless, odorless, and stable in liquids.

Sustamine is an ingredient that works on multiple levels to help rehydrate the body and sustain energy levels during exertion. Sustamine combines L-glutamine (the most important amino acid for stimulating muscle protein synthesis) and L-arginine (an amino acid needed for rebuilding your body's glycogen stores). Sustamine enhances performance and recovery in three primary ways. It helps:

- replace lost electrolytes and fluids
- repair damaged muscle proteins
- refill the body's energy stores

For more information on Sustamine, visit www.sustamine.com.

About Kyowa Hakko USA

Kyowa Hakko USA 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, and Setria Glutathione, as well as Sustamine L-alanyl-L-glutamine. For more information, visit http://www.kyowa-usa.com.

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

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Emerson Ecologics Launches Practitioner Resource Center for Integrative Health-Care Providers

Emerson Ecologics recently unveiled its newly designed Practitioner Resource Center, a full suite of clinical and business tools, resources, and education designed to help integrative health-care providers find success as healers *and* business owners.

The Practitioner Resource Center includes a rich variety of materials that can help health-care providers stay up to date on clinical knowledge and treatment plans, improve patient compliance, learn new strategies for growing their practice, and more.

"We've always been committed to helping our customers succeed as integrative health-care practitioners, and our newly designed Practitioner Resource Center is an extension of that commitment," said Dr. Jaclyn Chasse, medical director for Emerson Ecologics. "We recognize how busy our customers are, so our educational resources and materials are available in many different formats. And the majority of what we offer is available free of charge."

The Practitioner Resource Center offers clinical references, FAQs, peer-to-peer support via e-mail or phone, educational webinars, detailed product literature, the IGNITE series of business-oriented workshops, and more. Sample resources include:

- dietary and lifestyle recommendations for specific health conditions
- online databases listing drug depletions and interactions
- personalized answers to questions about integrative health treatments from Emerson's medical education team
- summaries of selected clinical research on select dietary supplement ingredients
- educational materials and webinars designed to help practitioners grow their business and attract new patients
- active compounds, suggested dosage, and potential interactions for botanical herbs
- calendar, links, and resources designed to help practitioners stay on top of industry research and/or maintain professional credentials
- suggested dosage and potential interactions for vitamins and supplements

To learn more about Emerson Ecologics, visit emersonecologics.com.

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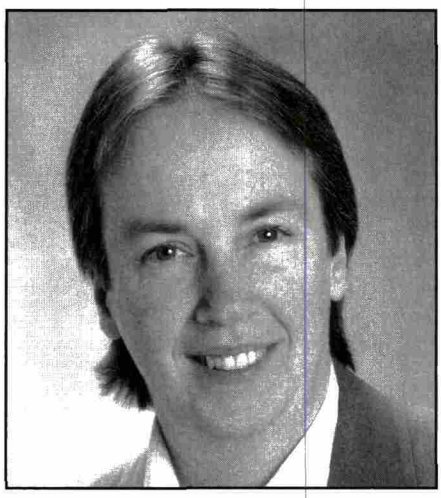

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Sample Treatment Strategies in Women's Health

For this month's column, I have decided to offer some of my best sample treatment plans for some select women's health issues. It is assumed that we treat the individual patient, but with diagnosed medical conditions, we have the advantage of using longstanding historical therapies, reliable empirical medicine, and modern evidence-based therapies for condition-specific issues with some expectation of reproducible results. We can then individualize our overall treatment approach based on the multitude of considerations for each patient. I offer these core sample treatment plans that can be considered an optimistic option for all of these selected conditions. Individuals with multiple health-care problems and important individual subjective and objective findings can then be addressed with the insight and experience of each practitioner.

Low-Grade Cervical Dysplasia

6-month treatment plan:

- Folic acid: 10 mg/day
- Diindolylmethane (DIM): 200–300 mg/day
- *Coriolus versicolor*: 3000 mg/day
- Oral green tea extract: 1 capsule/day
- The first 16 weeks of the 6 months: compounded 15% green tea suppositories from a compounding pharmacy, twice weekly for 16 weeks.

Polycystic Ovarian Syndrome

- High-protein/low-carb diet, whole-foods diet
- Flaxseeds, ground: 1–2 tbsp/day (preferably in smoothie with whey-protein powder as one meal replacement)
- Exercise: aerobic 60 minutes 6×/week, strength-train 2–3 times/week
- Soy powder: 30 g protein/30–90 mg isoflavones
- Chromium: 1000 mcg/day
- Nettle root: 400 mg/day
- Green tea extract: 1–2 caps per day
- Spearmint tea: 1 cup twice per day
- Fish oils 4 g/day (ratio 1.49:1 EPA/DHA)
- N-acetylcysteine: 600 mg 3× daily
- Consider:
  - Fenugreek: 25 g/day
  - Black cohosh: 40 mg/day for 10 days/month day 15–24
  - Licorice root extract
  - Vitamin D: 4000 IU per day

Acute Dysmenorrhea (Menstrual Cramps)

- 250 mg ginger capsules 4×/daily starting 3 days before onset and on days 1, 2, and 3 of menses
- Niacin 100 mg every 2–3 hours
- Consider:
  - Valerian: 255 mg capsules 3 times daily for first 3 days of menses
  - Cramp bark capsules or tincture: 2 caps or 1 tsp every 3 hours

Chronic Primary Dysmenorrhea (Menstrual Cramps)

- Regular exercise
- Diet: coldwater fish, fruits, caffeine, vegetables, nuts/seeds
- Fish oils: 1080 mg EPA + 720 mg DHA daily
- Pine bark: 100 mg per day
- Consider: black cohosh, wild yam, milk thistle, dandelion root, cramp bark, vitamin E, niacin
- Progesterone cream: ¼ tsp (20–40 mg) twice daily (or higher dose with oral micronized progesterone 100–200 mg before bed) days 15–26

Chronic Secondary Dysmenorrhea (Endometriosis)

- Diet:
  - Garlic, onions, curries, coldwater fish, fruits, veggies, nuts/seeds
  - Decrease saturated fats, sugar, salt, caffeine
- EPA 1080 mg/DHA 720 mg
- Vitamin E: 400 IU per day
- Vitamin C: 3–6 g/day
- Carotenes: 50,000–150,000 IU daily
- Selenium: 200 mcg twice daily
- Pycnogenol: 60–100 mg/day

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- N-acetylcysteine: 500–600 mg three times daily
- Turmeric: 1000 mg 1–2× daily
- Oral micronized progesterone: 200 mg daily, days 15–26
- Consider: probiotics, lipotropics, cramp bark, or black haw

Chronic Recurring Migraine Headaches

- Determine and avoid food sensitivities
- Determine and reduce other triggers
- Increase anti-inflammatory foods
- Butterbur: 50 mg twice daily
- Magnesium: 600 mg daily
- Riboflavin: 400 mg/day
- 5-HTP: 200–600 mg daily before bed
- For premenstrual headaches: add estrogen patch once weekly, days 15 and 21
- Acetaminophen, ibuprofen, triptans, or other medications as needed for attacks

Yeast Vulvovaginitis

Acute

- Compounded boric acid: 600 mg suppositories twice daily for 3–7 days
- Oral yogurt: 8 oz daily and/or *Lactobacillus* species (e.g., *Lactobacillus rhamnosus, Lactobacillus reuteri*) combinations: 1–10 billion per day for 2–4 weeks

Chronic/Recurring

- Compounded boric acid: 600 mg suppositories twice for 2–4 weeks, then 1× daily during menses only for 4 consecutive months
- Oral yogurt: 8 oz daily and/or *Lactobacillus* species (e.g., *Lactobacillus rhamnosus* with *Lactobacillus reuteri*) combinations: 1–10 billion per day for 4 months
- Consider systemic: garlic, Oregon grape, goldenseal, vaginal *L. rhamnosus/reuteri*
- Intravaginal Rx drug regimen – consider one of the following:
  - Butoconazole: 2% cream 5 g (butoconazole 1 sustained-released) single intravaginal application
  - Clotrimazole: 1% cream (OTC): 5 g intravaginally for 7–14 days
  - Clotrimazole 100 mg vaginal tablet: 2 tablets for 3 days
  - Miconazole 2% cream (OTC): 5 g intravaginally for 7 days
  - Miconazole: 100 mg vaginal suppository (OTC): 1 suppository for 7 days
  - Miconazole: 200 mg vaginal suppository (OTC): 1 suppository for 3 days
  - Miconazole: 1200 mg vaginal suppository (OTC): 1 suppository for 1 day
  - Nystatin 100,000 unit vaginal tablet: 1 tablet for 14 days
  - Tioconazole 6.5% ointment (OTC): 5 g intravaginally in a single application
  - Terconazole 0.4% cream: 5 g intravaginally for 7 days
  - Terconazole 0.8% cream: 5 g intravaginally for 3 days
  - Terconazole 80 mg vaginal suppository: 1 suppository for three days
- Oral drug regimen – consider:
  - Fluconazole: 150 mg oral tablet: 1 tablet in a single dose

Acute Bacterial Vaginosis

Acute: Option A

- Vaginal vitamin C tablet (250 mg) × 6 days, then
- Boric acid 600 mg suppository 1/day × 10 days, then 1× weekly for 6 weeks
- *Lactobacillus* species (e.g., *Lactobacillus rhamnosus* with *Lactobacillus reuteri*) combinations: 1–10 billion per day for 4 months
- Systemic immune support: Oregon grape, goldenseal; vitamin D; low-starchy-carb diet

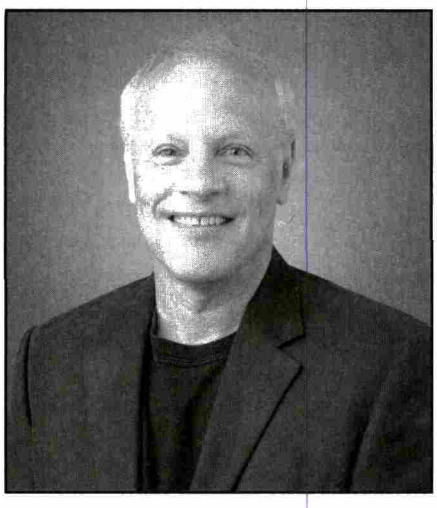
*Acute: Option B – **One** of the Following:*

- Metronidazole: 500 mg b.i.d. × 7–10 days
- My usual first choice: metronidazole vaginal gel 0.75% b.i.d. for 5–10 days
- Clindamycin 300 mg b.i.d. × 7 days
- Clindamycin cream 2% vaginally × 7 nights
- Ampicillin, doxycycline, sulfonamide creams with then 1 month of oral *L. reuteri/L. rhamnosus* capsules 1–10 billion/day

Chronic/Recurring Bacterial Vaginosis

- Insert vaginal vitamin C suppository nightly for 6 nights
- Then follow with boric acid 600 mg compounded suppositories or capsules nightly for 1 week then 1–2×/ weekly for 3–6 months
- Low-glycemic-index diet
- Vitamin D: 4000 IU daily
- Oral *L. rhamnosus/L. reuteri:* 1–10 billion daily for 4–6 months
- Consider:
  - vaginal metronidazole once weekly for 6 months
  - Vaginal estrogen in peri- or postmenopausal woman twice weekly

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. ◆



Folic Acid Versus Methylfolate

Folic acid (pteroylglutamic acid) is an important nutrient that has multiple functions in the body. It plays a role in the synthesis of DNA and RNA, and is also involved in homocysteine and vitamin B12 metabolism and in the functioning of the central nervous system and immune system. Folic acid supplementation has been shown to be effective for preventing neural tube defects and strokes. In some cases, it is also useful for the prevention or treatment of migraines, restless legs syndrome, osteoporosis, depression and other psychiatric disorders, psoriasis, gingivitis, cervical dysplasia, and certain other conditions. While folic acid itself is biologically inactive, it is converted in vivo to various biologically active folates, including 5-methyltetrahydrofolate (also called methylfolate or L-methylfolate) and 5,10-methylenetetrahydrofolate.

The nomenclature used to describe various folates is somewhat confusing. To a chemist, *folate* refers to the salt of folic acid. However, many nutritionists use the terms *folate* and *folates* to denote a spectrum of food-derived and biologically active endogenous compounds. In the discussion below, the nutritionist's terminology will be used, and folic acid will also be included as a folate compound.

Folate compounds that are commercially available include folic acid, methylfolate (also known as L-methylfolate, 5-MTHF, and 5-methyltetrahydrofolate), and folinic acid (5-formyl tetrahydrofolate). Folic acid is used most widely, because the vast majority of studies demonstrating clinical benefits of folates have used folic acid, and because it is chemically stable and relatively inexpensive. Folinic acid is used primarily in combination with certain anticancer drugs. Folinic acid is also an effective treatment for cerebral folate deficiency, a condition characterized by impaired transport of other folates across the blood–brain barrier. Methylfolate in relatively large doses (15 mg per day) has been found to be an effective adjunctive treatment for depression in patients who failed to respond to antidepressant medication alone.

Potential Advantages of Methylfolate

Recently, it has been argued that methylfolate is preferable to folic acid as a nutritional supplement. Some manufacturers have replaced folic acid with methylfolate in their multivitamin products, and some practitioners are of the opinion that products containing folic acid should not be used. One concern about folic acid is that it does not occur naturally in the body, and that people who take it have measurable concentrations of unmetabolized folic acid in their body. While unmetabolized folic acid has not been clearly shown to have deleterious effects, a few studies have linked folic acid supplementation to an increase risk of cancer, and the possibility that this effect is due to unmetabolized folic acid has not been ruled out. Another concern about folic acid is that some people, such as the 5% to 15% of the population that is homozygous for the 677C→T polymorphism of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, might have difficulty converting folic acid to its biologically active form, and therefore might not benefit sufficiently from folic acid supplementation. In addition, methylfolate appears to be somewhat more bioavailable than folic acid, in that it raises plasma and erythrocyte folate levels to a greater extent than does folic acid.[1,2] Furthermore, methylfolate is less likely than folic acid to mask the laboratory diagnosis of vitamin B12 deficiency.[3] It has also been argued that methylfolate is more effective than folic acid for lowering homocysteine levels. However, while one study showed a small but statistically significant advantage of methylfolate over folic acid, three other studies found that the homocysteine-lowering effect of these compounds did not differ significantly.[4–7]

Evidence Is Not Sufficient to Justify Switching to Methylfolate

After reviewing the available evidence, I have concluded that, despite some potential advantages of methylfolate,

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there is not sufficient evidence to justify routinely using it instead of folic acid. That conclusion is based on two main points. First, as mentioned above, the vast majority of the research demonstrating clinical benefits of folates has used folic acid. While a biologically active form of folate might theoretically be more effective than a precursor molecule, we do not know enough about how methylfolate as a supplement is transported and utilized in our cells and tissues to make assumptions about its comparative clinical efficacy. Randomized controlled trials are needed to determine whether methylfolate is more effective, equally effective, or less effective than folic acid for the prevention of neural tube defects and strokes, and for the prevention and treatment of other folate-responsive conditions.

Second, methylfolate is less stable than folic acid, a factor that could be particularly important when methylfolate is included in a multivitamin-multimineral preparation. Some compounds present in micronutrient formulations (such as vitamin C, copper, and thiamine) can react with and degrade other nutrients in the product, leading to a reduction in nutritional value and to the formation of potentially harmful degradation products. These types of reactions have been demonstrated to occur with vitamin B12; whether they also occur with methylfolate has not apparently been investigated.[8]

Folates and the MTHFR C677T Polymorphism

With respect to the subset of the population that is homozygous for the MTHFR C677T genotype, the impairment of methylation of folic acid to its biologically active form is relative rather than absolute, and can apparently be overcome in most cases by supplementing with a modest dose of folic acid. For example, in one study, 41 patients with persistently elevated plasma homocysteine levels (approximately 75% of whom were homozygous for the MTHFR C677T polymorphism) were treated with 0.2 mg per day of folic acid. Plasma homocysteine levels fell in all but 2 cases within 7 weeks, and became normal within 7 months in 21 of 37 cases. Most of the remaining patients obtained normal homocysteine levels after taking 5 mg per day of folic acid for 7 weeks.[9] In another study of patients with hyperhomocysteinemia who were treated with 5 mg per day of folic acid, the mean plasma homocysteine concentration fell by 40% among those who were homozygous for the MTHFR C677T genotype, but only by 23% among those with the CT genotype and by 10% in those with the CC genotype.[10] In a study of people with elevated homocysteine levels and homozygosity for the MTHFR C677T genotype, 200 μg per day of folic acid tended to be more effective than 200 μg per day of methylfolate for lowering homocysteine levels.[7] Taken together, these studies suggest that people who are homozygous for the MTHFR C677T genotype have a higher-than-normal folic acid requirement, but the studies do not support the claim made by some that folic acid supplementation is ineffective in people with the TT genotype or that methylfolate is a necessary or desirable alternative to folic acid in these individuals.

Folates and Depression

It has also been claimed that methylfolate is the preferred form of folate to treat depression, but there is no published research to support that assertion. In one study, 15 mg per day of methylfolate as an adjunct to antidepressants was beneficial, whereas 7.5 mg per day was ineffective.[11] In contrast, a double-blind trial found that supplementation with 0.5 mg of folic acid per day increased the efficacy and reduced the side effects of fluoxetine in depressed women. The same dose of folic acid was ineffective in men, possibly because men have a higher dosage requirement, based on their greater body weight.[12] Another study found that 5 mg of folic acid per day was significantly more effective than 1.5 mg per day as an adjunct to antidepressant medication.[13] Thus, daily doses of 0.5 mg and 5 mg of folic acid appeared to be beneficial, whereas a daily dose of 7.5 mg of methylfolate was not. These studies did not directly compare methylfolate and folic acid, and the patient populations may also not be comparable. However, the results are consistent with the possibility that folic acid is at least as potent as methylfolate in the treatment of depression. Moreover, in the study that used methylfolate, the presence of the MTHFR 677 CT/TT genotype was not significantly associated with a greater response to methylfolate.[14] That observation does not support the claim made by some people that having one or two 677T alleles predicts the need for methylfolate.

Folates and Cancer

With regard to folic acid and cancer, 2 randomized controlled trials found a significant increase in cancer incidence among people who received folic acid supplements.[15,16] However, both of those trials were post hoc analyses of studies that were not designed to examine the relationship between folic acid and cancer. The results of post hoc analyses must be interpreted with caution, and researchers generally consider these types of studies to be "hypothesis generating" rather than proof of an effect. More recently, 3 different meta-analyses of 10 to 13 randomized controlled trials found that folic acid supplementation was associated with a non-statistically significant 5% to 7%

increase in cancer incidence.[17–19] Some investigators have suggested that in the short term, folic acid may accelerate the clinical expression of cancers that are already present, but in the long term it may prevent the development of cancer by enhancing immune function and by preventing DNA from mutating.[20] While questions regarding folic acid supplements and cancer remain unresolved, there is at present no clear evidence that methylfolate is safer than folic acid with regard to cancer risk.

Conclusion

Additional research is needed to determine how methylfolate compares with folic acid in terms of safety and efficacy. At present, routinely substituting folic acid with methylfolate, particularly in multiple-micronutrient products, is not supported by the available evidence.

Alan R. Gaby, MD

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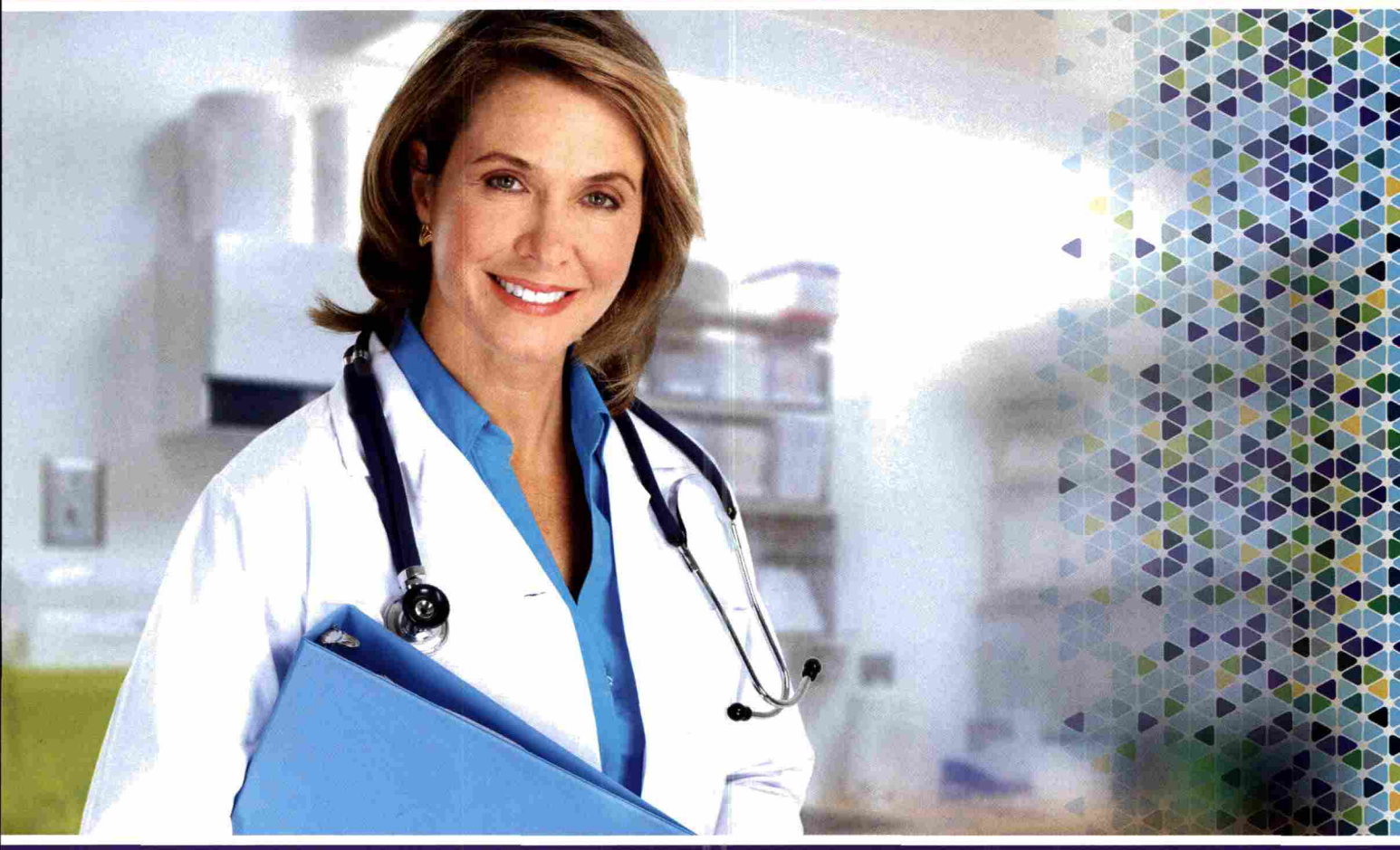

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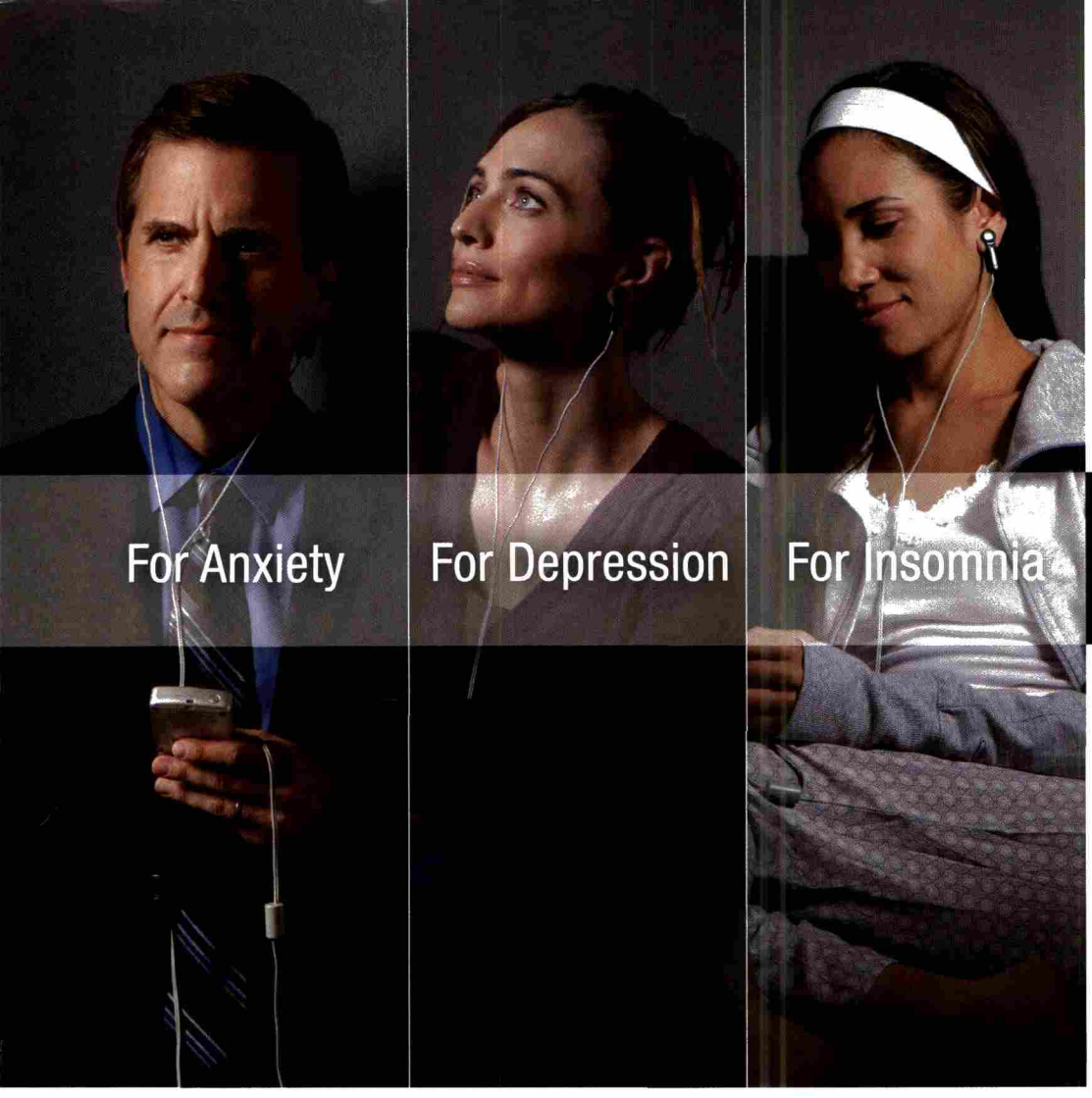

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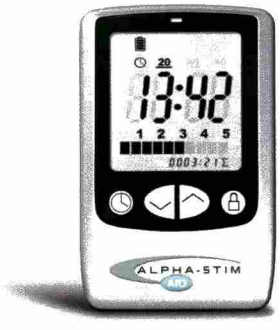

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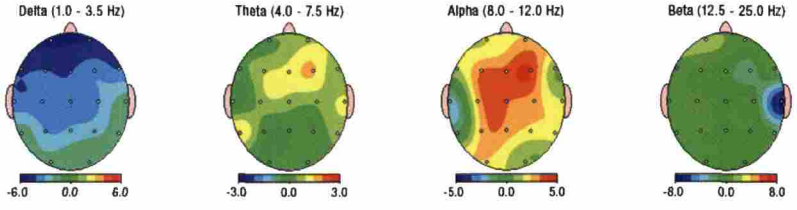

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*Kennerly R. Changes in quantitative EEG and low resolution tomography following cranial electrotherapy stimulation. PhD Dissertation, the University of North Texas. 2006;529 pp., 81 tables, 233 figures, 171 references.

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